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GUIDANCE FOR PERFORMING AGGREGATE EXPOSURE AND RISK ASSESSMENTS

OFFICE OF PESTICIDE PROGRAMS
ENVIRONMENTAL PROTECTION AGENCY
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I. Introduction

A. Overview of Main Points

Aggregate exposure and risk assessment involves the analysis of a single chemical exposure by multiple pathways of exposure. The pathways of exposure considered in this guidance document include the potential for pesticide residues in food, drinking water, and from residential, non-occupational pesticide use. Within an aggregate exposure assessment all relevant routes of exposure are analyzed. These include the oral route, dermal absorption, and inhalation route of exposure. The current practices for assessing aggregate exposure and risk typically include a mix of deterministic or point estimate data and distributional data; typically the food ingestion pathway is the only pathway for which there are sufficient distributional data to assess exposure and risk on a population basis. According to the *Interim* guidelines for performing aggregate exposure and risk assessment, most frequently the 'high-end' or upper bound point estimates from the drinking water and residential exposure pathways are added to a point on the distribution of food ingestion exposure, *e.g.*, the 99.9th percentile. However, the revised aggregate exposure assessment guidelines included in this document support a different approach to aggregate assessment. The revised approach suggests an analyst assess exposure on an individual-by-individual basis, culminating in a representative population of interest. In this way, the individual's temporal (*i.e.*, exposures via all pathways agree in time), spatial (*i.e.*, exposures via all pathways agree in place/location) and demographic (*i.e.*, exposures via all pathways agree in age/gender/ethnicity and other demographic characteristics) characteristics are consistent and reasonable. All 'linkages' of time, space and demographic characteristics should be made using supporting data. Using this approach, a distribution of total exposure to (many) individuals in a population of interest can be created. Distributional data analysis is preferred as this tool allows an aggregate exposure assessor to more fully understand the uncertainty and variability inherent in the data set. The adherence to the use of distributional data sets comprised of the aggregate exposures to (many) individuals in the population of interest and the suggestion that the individual's aggregate exposure be consistent in temporal, spatial and demographic characteristics is central to this guidance document.

B. Regulatory Background

Pesticides are regulated under both the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetics Act (FFDCA). In 1996, Congress passed the Food Quality Protection Act (FQPA) which amended both FIFRA and FFDCA. Through these laws, EPA evaluates risks posed by the use of each pesticide to make a determination of safety. The FQPA requires that the Agency consider aggregate exposure in its decision making. Section 408(b)(2)(ii) of FFDCA requires EPA to make a finding for each tolerance or tolerance exemption "that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." Section 408(b)(2)(C)(ii)(I) states that the Agency must find "there is a reasonable certainty that no harm will result to infants and children

from aggregate exposure to the pesticide chemical residues..." Finally, Section 408(b)(2)(D)(vi) directs EPA, when making tolerance decisions, to consider "aggregate exposure levels...to the pesticide chemical residue...including dietary exposure and exposure from other non-occupational sources."

Under FIFRA, EPA may register a pesticide for sale and distribution only if the use of the pesticide will not cause unreasonable adverse effects on the environment. This document explains the definition and implementation of aggregate exposure analysis at EPA and expands upon the *Interim Approach Paper for the March 1997 Scientific Advisory Panel* (US EPA, 1997c). The pursuit of information, methods, and results of aggregate exposure assessment described in this paper allows EPA to more fully and realistically evaluate the potential exposure of individuals and the population to pesticides in the environment. EPA strongly believes that enhanced methods for assessing the aggregate exposure described in this document will substantially improve protection of public health.

The Office of Pesticides Programs (OPP) is developing a series of guidance documents addressing new facets of the risk assessment process included in the FQPA. In particular, this document relies heavily on the *Exposure Factors Handbook* (USEPA, 1997b), the *Residential SOPs* (USEPA, 1997a), the *Interim Guidance for Conducting Aggregate Exposure and Risk Assessments* (Stasikowski, 1997) and *Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs* (USEPA, 1998c). In February 1999, the Scientific Advisory Panel (SAP) reviewed and commented on the draft *Guidance for Performing Aggregate Exposure and Risk Assessments*. The SAP comments to this draft document and the EPA response are in a separate document. SAP comments and recommendations have been considered in this revision.

C. Scope and Organization of Document

This document describes the overall framework and the general principles and steps to performing an aggregate exposure and risk assessment. Aggregate exposure and risk assessments are restricted to the analysis of the exposures and resulting risks from a single chemical by multiple routes. The routes considered at this time are oral (from food, drinking water, and residential pathway scenarios), inhalation (residential pathway), and dermal (residential pathway). This guidance does not fully investigate the data needed to describe the interdependencies and linkages between and among pathways of possible exposure. EPA realizes that the investigation is on-going and that further work is needed in this area to produce a fully refined, aggregate exposure analysis.

EPA acknowledges the need to assess exposures from non-pesticidal uses of pesticide chemicals. However, at this time the tools and methods available to do so are extremely limited. The Office of Pesticide Programs will work to develop science policy detailing the way in which aggregate exposure assessment may be performed for non-pesticidal chemicals as well as define the data needed to make the assessment. At this time, data are very limited for exposure estimation, and,

therefore, risk assessment for nonpesticidal uses of pesticide chemicals. Although, this paper does not directly address the aggregate assessment of non-pesticidal uses of pesticide chemicals, OPP believes the following methodology could also be adapted for the inclusion of non-pesticidal uses in an aggregate exposure assessment. EPA is interested in comments concerning the methodologies to be developed, the data required and its sources, and the ways in which exposure to non-pesticidal uses of a chemical can be included in an aggregate assessment.

This document is organized to first provide a view of current practices and data sources utilized in conducting aggregate exposure analysis (Section II), combining probabilistic (food pathway only at this time) and deterministic treatment of data. This initial section includes a pathway-specific set of comments on important points concerning the current methods to performing aggregate exposure and risk assessment. Section III provides a general framework and set of key concepts for the refinements to aggregate exposure and risk assessment put forth in this guidance document. Pathway-specific considerations based upon these revised guidelines are next discussed. Section IV presents the standard procedure to performing aggregate exposure and risk assessment, the basis of which is the *Interim Guidelines for Conducting Aggregate Exposure and Risk Assessment*. Following this section there are recommendations for future data and research needs (Section V) as well as an acknowledgment of the limitations in conducting aggregate exposure assessments (Section VI). The last section of the document, Section VII, describes the needs for model validation and verification, a vital part of evaluating aggregate exposure risk assessment model and methods, as assumptions, uncertainties, and variabilities imbedded in any model and/or method can be significant to the outcome of the assessment.

Lastly, questions are presented to the public concerning the framework and general steps in performing aggregate exposure and risk assessment. The appendices include a set of tables detailing some of the basic tenants of the *Interim* (current) approach to aggregate exposure assessment as well as a Glossary of terms.

D. Key Definitions

Some of the terms commonly used in this document are defined below and also appear in the Glossary:

1. Aggregate Dose - the amount of a substance available for interaction with metabolic processes or biologically significant receptors from multiple routes of exposure.

2. Aggregate Exposure -- the amount of a chemical available at the biological exchange boundaries (*e.g.*, respiratory tract, gastrointestinal tract, skin) for all routes of exposure.

3. Aggregate Risk - the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a single substance.

4. Exposure Scenario - a combination of facts, assumptions, and inferences that define a discrete

situation or activity where potential exposures may occur.

5. *Pathway* -- the physical course a substance takes from the source to the organism exposed, *e.g.*, food ingestion. Also called exposure pathway.

6. *Route* -- the way a substance enters an organism after contact, *e.g.*, inhalation. Also called exposure route.

II. Current Practices for Aggregate Exposure and Risk Assessment

Traditionally in performing risk assessments, OPP has treated exposures from different pathways as independent events, *i.e.*, one individual is exposed to one pesticide via a single pathway at a single point in time. However, in the real world, exposures to pesticides do not occur as single events, rather as a series of sequential or simultaneous events that are linked in time and place. By performing aggregate assessment (single chemical, multiple pathway/routes), OPP's exposure and risk assessments are expected to move closer to describing the pattern of exposure actually encountered by people in the real world.

Prior to combining exposures from multiple pathways into one aggregate risk measure, the magnitude of both exposure and risk for each pathway, route and exposure scenario will be calculated. In this section, an overview is presented for current methods to assess food, drinking water, and residential exposure and risk. It is important to fully understand the data sources, model capabilities and limitations, and robustness of data available for each of the three pathways of exposure. Relevant points from the toxicological endpoint selection process is also described. Subsequent to a review of the current, *Interim* practices for assessing aggregate exposure and risk, the revised guidance is presented.

A. Interim Aggregate Assessment Guidance: Current Practice

The Office of Pesticide Programs currently conducts aggregate exposure and risk assessments using procedures outlined in SOP 97.2 *Interim Guidance for Conducting Aggregate Exposure and Risk Assessments (*Stasikowski, 1997a*)*. The interim guidance was developed from material presented to the Scientific Advisory Panel (SAP) in March 1997. This document describes factors to consider when aggregating exposures or risks and methods for using toxicity endpoints in the aggregate risk assessment, among other things. The *Interim Guidance* is briefly summarized here; however, specific steps are not provided. Appendix I delineates, in tabular form, the source, route, pathway and toxicological information utilized for the (five) types of aggregate exposure and risk assessment performed in OPP under the *Interim Guidelines*.

Before considering the ways in which aggregate exposure and risk are currently assessed, it is important to understand deterministic and probabilistic treatment of data. A deterministic approach uses point estimates, *i.e.*, single maximum values or average values, to represent input

variables in the exposure model. This approach does not consider the range of potential exposures incurred by members of a population. A distribution can be used to describe the potential or probability of exposure to individuals within a population.

Currently, there are three possible combinations of data types in performing an aggregate exposure and risk assessment. First, an assessment could be entirely deterministic, *i.e.*, each pathway of exposure is estimated using the available data for an exposure variable as point estimates. This is usually considered a screening level assessment. Second, the three pathways considered in aggregate exposure assessment may include both probabilistic and deterministic assessments of exposure, the former describing exposure as a distribution for a given population, and the latter utilizing point estimates to calculate a single estimate of exposure. Typically, the food exposure pathway is estimated on a population basis using probabilistic techniques based on distributions of residue and consumption data for specific food items, while the residential and drinking water exposure pathways reflect an event exposure utilizing point estimates. Third, all three pathways might be described using probabilistic techniques. Clearly, the latter approach is the ideal case because all pathways are more fully described and the assessor has a much better sense of the variability and sources of uncertainty in the assessment. In this way, too, an assessor can gain a much clearer sense of where additional data would be most useful in further refining risk estimates.

In essence, the treatment of the first and second data-type scenarios, complete deterministic estimates of exposure and a combination of deterministic and probabilistic estimates of exposure for the three pathways in an aggregate exposure assessment, are the same. That is, a percentile for regulatory decision-making (*e.g.*, the 99.9th percentile in probabilistic (one-day) food exposure assessment) would be chosen, and that point included with the other pathway-specific point estimates would be included in the aggregate assessment. Because it is an anticipated component of the Revised Guidelines, the ways in which the three pathways of exposure would be combined when all three are described using distributional data will be addressed in this paper under Section IV *How to Perform Revised Aggregate Exposure and Risk Assessment*.

The *Interim Guidelines* describe five general durations of exposure. They are: acute (relevant for one-day exposure scenarios), short-term (relevant for 1-7 day exposure scenarios), intermediate term (relevant for 7-90 day exposure scenarios), chronic/long-term (relevant for exposures greater than 6 months in duration), and, cancer (relevant for lifetime exposures) using the Q_1* approach. Procedures fir aggregating specific pathways are based on exposure durations. Acute aggregate risk assessments combine dietary exposures for food and water only. Short-term and intermediate term aggregate risk assessments are done only when a potential for residential exposure exist. Chronic aggregate risk assessments are performed for long-term durations of exposure. The cancer aggregate assessment assumes that any amount of exposure will lead to some degree of risk. Most simply, under the *Interim Approach* to aggregate exposure and risk assessment, either the deterministic point estimate or the percentile of exposure value (*e.g.*, 99.9th%) for each exposure pathway is aggregated by adding the pathway specific exposure values, while correcting for the route of entry. (See Step 5 Aggregate Risk Index (ARI).)

Both current and future practices dictate that proper selection of the hazard endpoint for each route of exposure is essential to the accurate performance of aggregate assessment. When assessing exposures from food and drinking water, the oral route is of concern and, therefore, an oral toxicological study is appropriate for use in defining the hazard endpoint. When reviewing exposure potential from the residential (non-occupational) exposure scenarios, either oral, dermal, inhalation, or all three, may be needed, depending on the residential pesticide approved label uses and defined scenarios. Tables describing appropriate uses of hazard assessment studies for each route and pathway included in an aggregate assessment are provided in Appendix 1. The following sub-section describes basis for toxicological endpoint selection in aggregate exposure and risk assessment.

B. Toxicological Endpoint Selection: Current Practice

Examination of the toxicity data requires the concurrent assessment of which scenarios will be represented in the assessment. Specifically, it is important to determine the time period over which an individual may be exposed, so that exposure estimates are compared with toxicity studies of similar duration. If several days of continual dosing are required to establish the effect, it would be inappropriate to compare the exposure over a single day. Rather, a sustained time period of exposure would be necessary to indicate that an adverse effect in humans is likely. Similarly, a toxic effect that is established following a single dose or one day's exposure may indicate the need to evaluate exposure over a single day time period for the assessment. Where exposure scenarios do not produce the potential for an adverse effect, those exposure scenarios may be eliminated from the assessment. However, this should be done cautiously because the final exposure which is analyzed in the assessment may be the accumulation of many small exposures from many pathways. An analyst may consider many different toxicological factors relevant to each route of exposure when performing an aggregate assessment. (See Appendix 1 for details.) Also, useful terms in understanding and interpreting the toxicological endpoint selection for an aggregate risk assessment are provided the Glossary at the end of this document.

C. Food Exposure Assessments: Current Practice

Food exposure scenarios are typically evaluated on the basis of short-term, acute, and long-term, chronic time frames of exposure. For both time frames, a tiered approach is used to introduce refinements to the assessment that reduce conservatism and attempt to be more reflective of the actual exposure. Advancing through the tiered assessment process requires additional use-related, and other, data concerning each commodity. In most cases, refinements may be possible for some proportion of the commodities undergoing evaluation, but not for others. In such cases, deterministic estimates may be made for some food commodities in the assessment and more refined probabilistic assessments using distributional data sets may be used for other commodities and combined with the point estimates from deterministic assessments.

The tiering criteria for the conduct of acute dietary (food only) risk assessments is outlined in a previously released policy document *Interim Office Policy for Performing Acute Dietary Risk*

Assessment (Irene, 1996). OPP defines Tiers 1 and 2 as using residue input data as point estimates in a deterministic assessment and Tiers 3 and 4 using distributions of residue input data in a probabilistic assessment. A Tier 1 food exposure assessment uses a single, high-end point residue estimate and a distribution of consumption data to provide a single, upper-bound (worst-case) point estimate of acute exposure. Tier 2 is the same as Tier 1, except that it uses a single, average residue data point (point estimate) for commodities which are typically mixed or blended. It provides a more realistic estimation of exposure than Tier 1 by considering average anticipated residues for food forms that are typically widely mixed prior to consumption. Tier 3 uses a distribution of residue data points (adjusted using the maximum weighted average percent of crop treated) as well as a distribution of consumption data points. Tier 4 requires even more extensive data than Tier III (*e.g.*, single-serving market basket surveys, cooking studies, etc.), but provides the most representative exposure picture. However, it may not provide a lower exposure estimate than Tier III (Irene, 1996).

Chronic dietary exposure and risk assessments also use a tiered approach to gain the most refined estimate possible. All tiers of the chronic assessment produce estimates of dietary (food only) risk that are based on average consumption of foods (which may be categorized by population and age and other sub-groups) and average of residues in specific foods. Chronic assessments currently conducted by OPP are deterministic (use of point estimates) in nature. Tier 1 of a chronic dietary exposure and risk assessment uses tolerance level estimates of the magnitude of the residue and assumes that 100% of the crop is treated. Tier 2 is the same as a Tier 1 chronic dietary assessment, but data on the national (weighted average) percent of the crop treated is incorporated into the assessment. Tier 3 uses average residue from field trials or monitoring data, incorporates the percent of the crop which is treated, and incorporates commercial processing factors and uses refined livestock burden and milk, meat, poultry and eggs (MMPE) residue values. Tier 4 of a chronic dietary exposure and risk assessment may use any combination of market basket survey data (as average residue values) and incorporate cooking, residue decline, and residue degradation information, if available.

The primary source of food consumption data used in dietary risk assessments is the Continuing Survey of Food Intakes by Individuals (CSFII) (USDA, 1992) for the years 1988-1991. The CSFII is particularly well suited to the conduct of national level dietary risk assessments because it is statistically designed to sample individuals of all ages and ethnicities to permit a reflection of the appropriate demographics. It is also balanced so that all seasons of the year and regions of the country are represented. As subsequent surveys are translated to processed commodities for use in risk assessment, they will be used to update the dietary risk assessment process. EPA plans to use the latest CSFII data (1994-1996) and the Children's Supplemental survey of 1997 in early 2000.

Data on the residues of pesticides in foods are obtained from a variety of sources. Traditionally, the primary source of residue data in foods has been field trial data which must be submitted in support of the registration and reregistration of a pesticide. These data overestimate the residues that are likely to occur in food as actually consumed because they reflect the maximum application

rate and shortest pre-harvest interval, and represent residue levels "at the farmgate." Data that are more reflective of residues on foods as consumed are often available from monitoring data in which food samples are obtained closer to the dinner table in the chain of commerce and analyzed. These data come from federally funded surveys such as the Pesticide Data Program (PDP) conducted by the U.S. Department of Agriculture (USDA), and the Food and Drug Administration (FDA) Surveillance Monitoring data. These data are useful for refining chronic dietary assessments, and provide the best characterization of pesticide residues in or on foods consumed by the U.S. population.

D. Drinking Water Exposure Assessments: Current Practice

To estimate aggregate exposure to pesticide residues in drinking water, OPP uses the general policy outlined in the SOP 99.5 *Interim Guidance for Incorporating Drinking Water into Aggregate Risk Assessments* (Stasikowski, 1999). The registered uses and the potential for a pesticide to contaminate surface and ground waters are considered initially. If the use pattern and potential to contaminate water resources are such that there is no possible exposure to surface or ground waters, OPP concludes the pesticide will not impact drinking water residues, and exposure and risk to the pesticide in water are not included in the aggregate assessment. Frequently, this is the case for pesticides exclusively registered as baits or seed treatments and pesticides with import tolerances only.

If a pesticide has any potential to contaminate water resources based on use patterns, OPP uses water quality models to estimate the concentration of the pesticide in surface run-off and in shallow ground water. For the purposes of comparison to a drinking water level of comparison (DWLOC), the concentration estimates generated from the models are considered to be upper bounds on pesticide concentrations in drinking water obtained from surface and ground water sources. A DWLOC is the theoretical concentration of a pesticide in drinking water that would be an acceptable upper limit in light of the aggregate exposure to that pesticide from other sources (*i.e.*, food and residential use). OPP compares the model-generated concentration estimates for a pesticide in ground and surface water to levels of comparison in drinking water [calculated separately for different toxic effects where warranted, *i.e.*, for acute (one-day), chronic (long-term), or short-term and intermediate toxic effects]. If the model-estimated concentrations in ground and surface waters are less than the level of comparison in drinking water, OPP concludes with reasonable certainty that residues of the pesticide in drinking water from present uses do not contribute towards an aggregate level of exposure that exceeds a risk level of concern.

If the model estimates are greater than OPP's levels of comparison for drinking water (DWLOC), OPP refines its model estimates using more realistic information/assumptions and compares the refined estimates to levels of comparison for drinking water again. If the model estimates still exceed OPP's levels of comparison for the pesticide in drinking water, OPP obtains all available water quality monitoring data for the pesticide, and conducts an in-depth review of the data to determine if they are acceptable and reliable for use in quantitative drinking water exposure and

risk assessment. Some of the data sources reviewed include: 1) prospective monitoring studies designed to track a pesticide's movement into surface or groundwater from the point of application, 2) retrospective monitoring studies designed to provide information on general pesticides occurrence (examples include U.S.G.S. NAWQA database on ambient surface water and some groundwater), data collected under the Safe Drinking Water Act (SDWA) for approximately 25 pesticides in finished drinking water, data collected under the EPA National Well Survey (1990), and 3) pesticide specific data as collected by registrants (examples include the Acetochlor Registration Partnership (ARP), and surveys for atrazine in drinking water.

If the monitoring data are suitable, they are used to calculate aggregate exposure for use in a human health risk assessment. Average annual and maximum (peak) concentration values (point estimates) from localized monitoring data for the pesticide are used in deterministic chronic and acute exposure assessments, as appropriate, *i.e.*, usually average values are used in assessments concerned with exposures greater than one-day, and maximum values are used in exposure assessments of one-day's duration, respectively.

If the available water quality models' estimates are equal to or exceed OPP's levels of comparison for the pesticide in drinking water, and no appropriate monitoring data are available, OPP considers the entire risk picture for the pesticide and determines the appropriate action. That is, if exposure to the pesticide is above levels of concern from food and residential exposures, and drinking water impacts are indicated to be significant by the model estimates, a risk management decision may include a requirement for monitoring data to confirm the pesticide's presence in drinking water, or various other risk management options. Also, for those pesticides that fail the screening tiers and require detailed risk assessments, the preferred approach to the dietary (food+drinking water) portion of an aggregate exposure assessment is to combine a probabilistic drinking water exposure assessment with a probabilistic food exposure assessment. However, a probabilistic assessment of pesticide exposures in drinking water necessitates distributional data on a given pesticide in tap water, if the data are available.

Because pesticide contamination of water is localized, drinking water exposure assessments should be conducted on a localized basis, not a national basis. That is, the pesticide concentrations assigned to a specific individual on a given day should be characteristic of and consistent with that individual's water supply. It would make little sense, for example, to assign to an individual living in a small community in the Midwest during the spring, pesticide concentrations characteristic of a large northern city in the wintertime. As stated earlier, properly conducted aggregate exposure should reflect the appropriate dependancies and linkages and incorporate this information appropriately. The localized monitoring data can potentially be combined to create a regional risk assessment. Regional estimates generated in this way can then potentially be combined to create national estimates of the exposures.

E. Residential Exposure Assessments: Current Practice

Currently, OPP uses the *Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments* (USEPA 1997a) as guidance for conducting estimates of residential exposure. These SOPs identify approximately 15 common pesticide related use patterns/use sites (e.g., treatment of residential lawns, garden plants, etc.) that result in residential exposures. Each of these residential activities/use sites is further divided into handler and post-application categories. These are further divided by age group (*e.g.*, adult, toddler, *etc.*), route (oral, inhalation, dermal), and specific activity (e.g., incidental ingestion of soil, incidental ingestion from hand-to-mouth transfer). The left-hand side of Figure 1 illustrates these pathways and routes for residential lawns. These SOPs produce a point estimate of exposure for each assessed scenario.

The basic steps in performing a residential assessment are as follows:

- identify formulations, application rates, and sites of application (from labels);
- identify method of application;
- determine magnitude of exposure by route for the applicator;
- identify post-application exposure scenarios;
- determine magnitude of post-application exposures (accounting for overall residues and dissipation);
- determine duration of exposure (short-term, intermediate-term, and long-term)

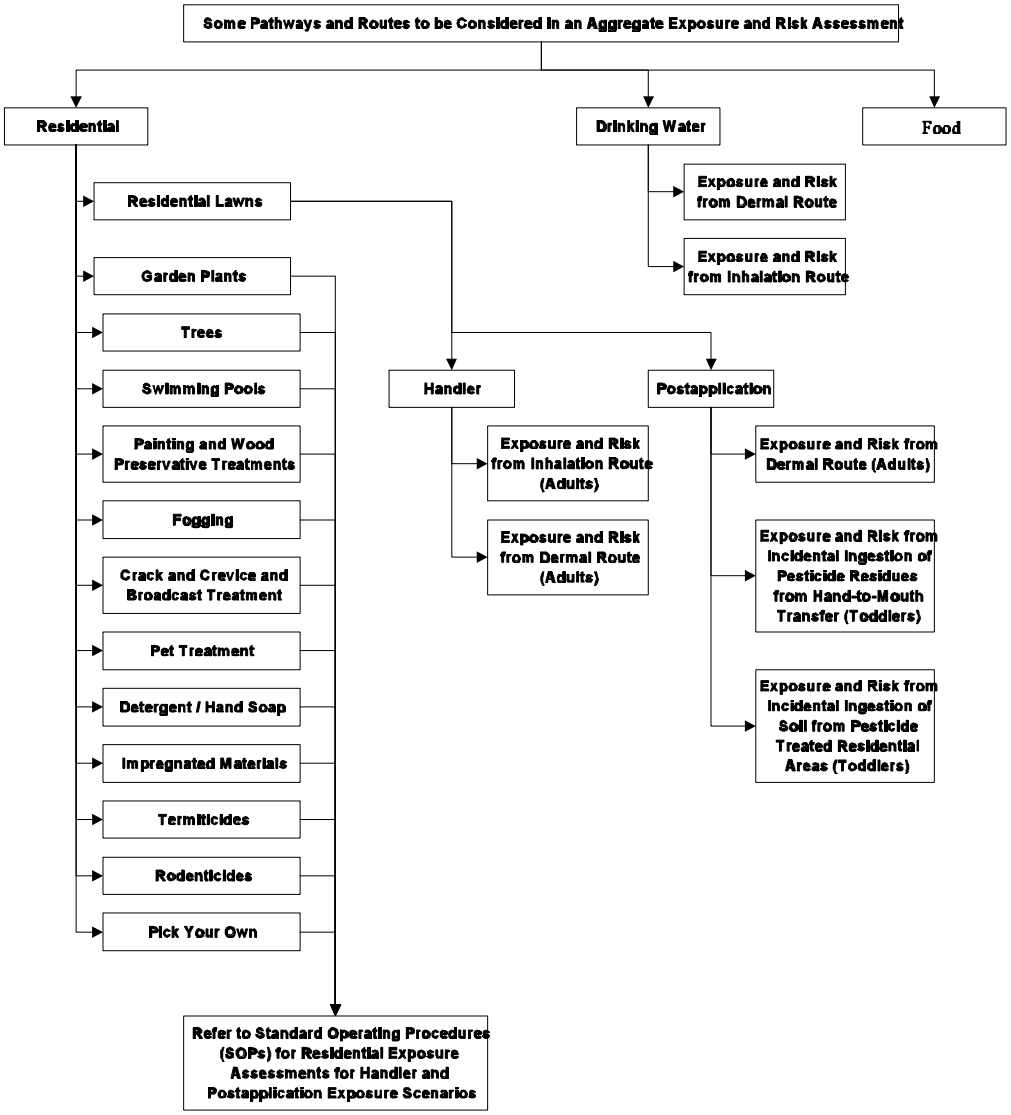
Additional details on the residential analytical methods, assumptions, and default values are described in the Residential SOPs (USEPA, 1997a). Note that the SOP's are undergoing revision and will be released in revised form.

Useful data for residential assessments are available from several sources. Data addressing non-dietary exposure have traditionally been required (under *Series 875 - Occupational and Residential Exposure Test Guidelines; Group A, Applicator Exposure; and, Group B, Post Application Exposure*) when certain toxicity and exposure criteria are met. Acutely toxic compounds in Acute Dermal Toxicity Category I and Acute Toxicity Category II, or greater, are triggers for applicator exposure and post-application exposure monitoring data requirements, respectively. Other adverse effects such as developmental or neurotoxicity are also considered, if results of those studies which show adverse effects are available.

Other sources include proprietary data submitted to the Agency to support residential uses of pesticides, and in a few cases published studies. However, for most non-dietary exposure assessments, surrogate data and screening-level (Tier I) assessments presented in the Residential SOPs (US EPA, 1997a) will be used.

If the estimates of residential exposure in combination with estimates of food exposure exceed the PAD or RfD, OPP determines the appropriate regulatory action. That is, if food and residential exposures are above the level of concern for a pesticide, a risk management decision may include a requirement for additional data and/or various other risk management options to reduce risk to acceptable levels.

Figure 1


Some Pathways and Routes to be Considered in an Aggregate Exposure and Risk Assessment
Residential
Drinking Water
Food
Exposure and Risk from Dermal Route
Exposure and Risk from Inhalation Route
Residential Lawns
Garden Plants
Trees
Swimming Pools
Painting and Wood Preservative Treatments
Fogging
Crack and Crevice and Broadcast Treatment
Pet Treatment
Detergent / Hand Soap
Impregnated Materials
Termiticides
Rodenticides
Pick Your Own
Handler
Postapplication
Exposure and Risk from Inhalation Route (Adults)
Exposure and Risk from Dermal Route (Adults)
Exposure and Risk from Dermal Route (Adults)
Exposure and Risk from Incidental Ingestion of Pesticide Residues from Hand-to-Mouth Transfer (Toddlers)
Exposure and Risk from Incidental Ingestion of Soil from Pesticide Treated Residential Areas (Toddlers)
Refer to Standard Operating Procedures (SOPs) for Residential Exposure Assessments for Handler and Postapplication Exposure Scenarios

III. Framework for (Revised) Aggregate Exposure and Risk Assessment

Current and revised practices for performing aggregate exposure and risk assessment use the same data sources, same data quality standards, and the same pathways of aggregation (food, drinking water, and residential). However, the revised practices look at new ways to frame the data and to combine existing sources. This discusses the revised framework for considering aggregate exposure and risk assessment while Section IV reviews the general steps to incorporate this new framework/approach.

A. Revised Approach to Aggregate Exposure and Risk Assessment

The fundamental difference between the current and revised approach to aggregate exposure assessment is the principle that exposure occurs to each individual in the population, individual by individual, ultimately combined into an assessment of the total exposure of the population. And, the aggregate exposures which occur to each individual in the population agree in temporal, spatial and demographic characteristics. Therefore, the revised approach to aggregate exposure and risk assessment focuses on the potential exposure to a single chemical by multiple routes to individuals in a population. Exposures to an individual in a population: 1) may occur by more than one route (i.e., oral, dermal and/or inhalation); 2) may originate from more than one source and/or pathway (*i.e*., food, drinking water, and residential); 3) occur within a time frame such that the chemical exposure overlaps correspond to the effective period of the adverse toxicological effect; 4) occur at a spatially relevant set of locations that correspond to an individual's potential exposure; and, 5) be demographically consistent.

For example, an assessment could be linked to certain types of residential use scenarios considering that the use of one product may increase the likelihood of using another product. Or conversely, the products may serve essentially the same purpose, such that the use of one will almost certainly preclude the use of the other. Aggregate exposure assessment is performed by developing a series of scenarios (based on/using existing data) in which the exposure scenarios correspond to the relevant characteristics of time and space, *e.g.*, an individual's activity patterns, and are based on the toxicological endpoints and exposure duration of significance. The development of individually focused exposure scenarios also helps prospectively to define populations of concern, and provide critical windows within time frames and routes of exposure that will be linked to toxicity endpoints. Focusing on the individual and then the population (or sub-population) of individuals, an assessor then builds the aggregate analysis.

These guidelines are meant to provide a framework for aggregate exposure and risk assessment based on assessing an individual in the population and then the population (or sub-population) as a whole. An analyst would likely take into consideration many case-specific pieces of information and employ judgement concerning the use of certain data in the step-wise performance of aggregate exposure and risk assessments. Therefore, a specific step-by-step set of instructions is not presented. Also, it is important to note that neither the current, interim practices for performing aggregate exposure and risk assessment, nor the following revised approach support

the use of any one particular percentile of exposure in regulatory decision-making, *e.g.*, 95th percentile of exposure. EPA will review all data included in an aggregate exposure and risk assessment and determine, on a case-by-case basis, the percentile of exposure to be used in making regulatory decisions for a particular chemical.

B. Key Concepts in Revised Approach

Certain key concepts and definitions are important to understand in the discussion of the revised approach to aggregate exposure and risk assessment. This section briefly describes these concepts and definitions, with more detailed treatment appearing later in the document and in the glossary. Additional information about general risk assessment concepts can be found in the following two documents: *Risk Assessment in the Federal Government: Managing the Process* (National Research Council, 1983) and *Science and Judgement in Risk Assessment* (National Research Council, 1994).

In review, aggregate exposure analysis refers to single chemical exposure via the dietary (oral route via food and drinking water) pathway and non-occupational (inhalation, dermal and/or oral route) pathways. At the time of the writing of this document, occupational exposure scenarios are not included in aggregate exposure and risk assessment. This document assumes aggregate exposure and risk are estimated using probabilistic assessment techniques, where data allow. The way in which multiple pathways can be aggregated using entirely distributional data is discussed in Section IV. The following section also includes a discussion of the ways in which deterministic and probabilistic data for the different pathways of exposure can be combined within an aggregate assessment.

The basic concept underlying aggregate exposure assessments is that exposure occurs to an individual. The integrity of the data concerning this exposed individual should be consistently maintained throughout the aggregate exposure assessment. Each of the individual "sub-assessments" should be linked back to the same person and the aggregate intake should reflect the food, drinking water, and residential intakes that are for the same individual at the same time, in the same place, and under the same demographic conditions. The assigned exposures to an individual should be internally consistent and appropriately reflect the dependencies and linkages that are inherent under different temporal and spatial exposure scenarios. In other words, the aggregation should be *simultaneously* temporally, spatially, and demographically specific, i.e., it should agree in time, place, and demographic characteristics (ILSI, 1998a).

1. Exposure to the Individual

Aggregate exposure assessments reflect the concept that exposure occurs to an individual, and, many individuals together comprise the aggregate exposure population (or sub-population). The integrity of the data concerning this exposed individual should be maintained throughout the aggregate exposure assessment. In other words, each of the individual "sub-assessments" investigating the food, drinking water and residential pathways of exposure, are linked back to the

same consistent “person.” Because exposures are based on the amount/dose received by a single individual, aggregate exposure assessments should take into account, to the extent data allow, the fact that an individual’s exposure is temporally, spatially and demographically intra-dependent. Exposure pathways to each individual can be matched to create a reasonable assessment of an individual who is part of the population of concern.

Aggregate exposure and risk assessments will be more realistic to the extent that the appropriate temporal, spatial, and demographic factors that affect exposure to an individual are understood and accounted for correctly. Examples of some of these factors include gender- and age-specific body weights, regional specific drinking water concentrations of the pesticide under consideration, seasonally-based pesticide residues in food, and frequency of residential pest control activity representative of housing type and regional location. When these data are not available, reasonable assumptions that do not underestimate exposure can be used. Once an aggregate exposure and risk assessment is completed for one individual and repeated for many individuals, population and sub-population distributions of total exposures and risk may be constructed by probabilistic techniques. Figure 2 illustrates the ways in which potential exposure to an individual are used in an aggregate assessment.

Figure 2: Exposure to an Individual in the Population

Example(s) of Individual Characteristics	***Dimension***	***Correlation for an Individual in the Population***
- Person's Age - Season of the Year	*Temporal*	- Age correlates with body weight/height, consumption pattern (record), inhalation rate - food (drinking water) consumption and residential pesticide application pattern consistent with season of year
- Location and type of home (urban area, region of country)	*Spatial*	- food consumption consistent with region of country - drinking water estimates consistent with region of country (rural or municipal water supply) - residential pesticide usage likely for region of country
- Gender - Socio-economic status (SES)	*Demographic*	- reproductive status consistent with age and gender - food (drinking water) consumption pattern (record) consistent with economic level - personal preferences, behaviors, and characteristics consistent with data on home pesticide usage and type of home
Individual Example: An individual which is part of a population of concern in an aggregate exposure and risk assessment is a 1-year old female, in New England, during the winter, in a rural location without municipal water (on rural well water), whose food consumption is selected from the range of records for the age 1-year old, who encounters potential residential pesticide use (exposure) consistent with a rural, New England location in the winter. She does not apply home pesticides, but may come in contact with pesticides by crawling on the floor. Body weight, height, surface area, inhalation and other biological determinants are consistent for a 1-year old.		

2. Exposure Interval and Event Correlation

Another key concept is that all exposure events occur over a specific interval of time. Pesticide use on one day may produce exposures to the same individual either for a brief period of time over the course of several days. One method of visualizing this is to consider exposures occurring on a calendar basis. For example, a homeowner uses an indoor fogger on Monday to treat a roach problem. Not only would home owner experience exposure to a pesticide on Monday, but

she would also experience exposures on subsequent days as the pesticide is distributed in the house and the pesticide residues decay. This scenario contrasts with a person who swims in a pool containing pesticide residue; the swimmer's exposure would be confined to the time at the pool. (The swimming pool exposure, however, might be repeated on subsequent days.)

When considering exposure events, it is important to consider their interactions. For example, an exposure event on one day may also produce or have some affect on exposure events on subsequent days. For example, if a homeowner uses an indoor fogger on one day to treat a roach problem, the inhabitants may also receive exposures on subsequent days as the pesticide is distributed in the house. As the pesticide decays with time, subsequent exposures (on subsequent days) would decline as well. On the other hand, if a homeowner uses an indoor fogger on one day, he or she is unlikely to use a fogger on the following day.

In addition, the assessment should appropriately incorporate linkages or correlations/associations (which can be either positive or negative) between use events. For example, in some cases the use of one product may affect the likelihood of using another product. This might be true with respect to products used for flea control: an indoor fogger, lawn care product, and a flea product for a pet might be more likely to be used simultaneously. In other cases, the products may serve essentially the same purpose, such that the use of one will almost certainly preclude the use of the other. Places of residence should be linked or otherwise correlated to a type of water source. It is much more likely, for example, that a residence located in a rural site in the Midwest will have a private well as a source of the household water supply than a residence in an urban location in the Northeast. In this case, the location of the residence should be linked through the use of existing data with the source of the water supply to appropriately incorporate real-world situations and ensure that unrealistic or unlikely combinations are appropriately discounted.

In developing a detailed exposure assessment to individuals in a population for a single chemical with a variety of use patterns, it is necessary to estimate the daily exposure of an individual to the exposure from each source on any given day. A calendar-based approach provides the ability to estimate daily exposure from multiple sources. Equally as important, this approach permits the incorporation of carryover from pesticide uses on previous days. Carryover reflects the dependence of exposures on successive days of residual pesticide resulting from previous applications. Carryover is particularly important in the evaluation of pesticides used in and around residences and similar sites. Residential application of a pesticide may occur on a single day, but exposures may continue for several days following application as the product degrades in the residential environment. Each succeeding day following application is anticipated to present a decreased exposure until the level returns to pre-exposure event levels. Multi-day exposures of this type can be reflected in a calendar-based model in the form of decay curves which model the decline in pesticides residues on the initial day over the next several days of the modeled year.

A calendar model also has the advantage of permitting evaluation of exposure over a variety of time frames for comparison to toxicity data of a comparable time course. OPP uses breakpoints for defining the time frames of interest for exposure assessment. Times of interest are typically

framed in terms of "acute" or "chronic" exposures. However, the calendar model will permit the use of rolling time frames of varying length to examine the entire spectrum of likely exposures for periods of exposure that exceed the safe level for the appropriate toxicity endpoint. An example of the use of a rolling time frame is selection of a two-week time interval over which to average exposure. The exposure for two weeks beginning on day 1 of the year (and proceeding through day 14) would be evaluated. Next, exposure for the two-week period beginning on day 2 (and proceeding through day 15) would be evaluated. Each of the 365-available rolling two-week periods for the year would be examined by moving the start date by one day on each pass.

3. Relevant Toxicological Information

One critical concept which is contained in both the *Interim Aggregate Guidelines* and these revised guidelines is the need to consider the relevant toxicological information for each route (and then pathway) of an individual's exposure. An individual's dose should be matched against relevant toxicological doses in terms of route, duration, and effect. For many compounds, the toxic effects are markedly different by one route and duration from those produced by a different route and duration. To produce an aggregate risk estimate, risk measures could be calculated separately for each route and duration for a given toxic effect for each individual in the population, and then combined to create a total population. A separate aggregate assessment could then be performed for each toxic effect of concern. For instances in which route-to-route extrapolation of toxicological dose are considered because of lack of route-specific data, the *Interim Guidelines for Aggregate Exposure and Risk Assessment* provide suggestions and methods for doing so.

C. Pathway-Specific Considerations before Aggregation

This section describes pathway-specific issues and guidance for performing aggregate exposure and risk assessment for individuals in a total population. These are specific issues to consider when performing the pathway-specific analysis prior to aggregation.

1. Food Pathway and Aggregation

Aggregate exposure scenarios may be developed beginning with the food exposure pathway. Because the body of information is more robust (*i.e.*, distributional data describing a range of specific pesticide residue values on specific food items are available) for this pathway compared to the other pathways, the development of the aggregate exposure scenarios could likely be driven in some measure by the information contained in the food consumption and residue database. As stated above, aggregate analysis should be performed on an individual basis in order to maintain the linkages and associations between consumption data and demographic data. Food consumption data files provide information on region of residence, season, and socio-economic status of the consumption survey respondents which may be useful in defining likely related residential and drinking water exposure scenarios. Similarly, differences in pesticide use and usage rate which are available from a variety of sources may also be related to region, and permit

development of more refined and focused individual-based aggregate risk assessments. Regional factors will also be important in selecting the appropriate drinking water data for use in the assessment.

An initial step in creating aggregate exposure scenarios is to identify the demographic profile of a sub-population upon which the assessment focuses. The age, gender and geographic location of the group included in the investigation of the food exposure pathway may also be linked with exposure scenarios in the other two pathways of exposure, which would incorporate appropriate assumptions concerning the likelihood and frequency of exposure events over time. The individual consumption records in the database linking the demographic and other descriptors would be used to simulate the consumption patterns of the population or sub-population of interest. The likelihood and frequency assumption for residential scenarios would be used to superimpose a pattern of residential exposures that would reasonably be expected to occur throughout the year for that individual in the population.

It is important to be aware that from the selection of an individual consumption record, other exposure scenarios may be more easily defined. For example, if the consumption record selected is an 8 month old female infant, in rural New England during the Springtime, this information would be used to select residential exposure scenarios that would be feasible for an infant in spring time in rural parts of New England. This record would not be used in comparison with a pesticide applicator residential exposure scenario because an infant would not likely be a pesticide applicator. In addition, probabilities that the relevant drinking water source for the infant in the northeast is private well water or municipal water would be assigned based on data on drinking water sources and the degree of urbanization for that region of the country.

2. Drinking Water Pathway and Aggregation

Specific issues in aggregating potential exposure to pesticides through drinking water also include spatial, temporal, micro-environment, and treatment-related considerations. Exposure to pesticides in drinking water is usually a localized or regionalized phenomenon driven by pesticide use patterns and local hydrologic and climatological conditions. Accordingly, it cannot be assumed that exposure to a pesticide in one location of the country will be the same for other locations. Drinking water exposures to individuals in a population from pesticides should be incorporated into aggregate exposure assessments on a localized basis. This step can be accomplished using distinct data sets collected in light of specific pesticide use patterns, when available. However, localized data sets are applicable only for that locale, *i.e.*, drinking water concentrations of products used in the corn belt would not be assumed for all individuals across the entire country, but only for individuals who may potentially be exposed in that locale. Also, pesticide impacts on drinking water are often seasonal in nature and are driven by time of application and the weather conditions present shortly after application. Therefore, temporal variation in pesticide concentrations in drinking water should be considered in any individual-based, aggregate exposure assessment for drinking water.

Many localized exposure assessments for drinking water may be performed on an individual-by-individual basis and combined into a population-based exposure assessment, and, then combined with individually correlated exposures determined for foods. Existing food exposure models could be used for different locales to incorporate the localized distribution of pesticide concentrations in drinking water. The quality of the localized exposure assessments for drinking water is dependent on the quality and availability of localized data sets for pesticides in tap water. Using localized drinking water data, an assessor could link a food consumption record from a respondent from a certain locale of the country with a localized drinking water data distribution.

Also, the impact of treatment should be considered in any drinking water exposure assessment, where data are available. Municipal drinking water facilities across the nation use a variety of treatment processes in delivering tap water to the public. Drinking water obtained from private wells is mostly untreated. Any aggregate exposure and risk assessment is generally not considered complete until the effects of treatment, where warranted, in whatever form (sedimentation, flocculation, chlorination, filtering through granular- or powder-activated carbon, etc.) have been included.

Situations may exist where specific sub-populations have a different potential for exposure through drinking water to a pesticide than the rest of the population. These situations may exist where a pesticide's use pattern is very narrow, *e.g.*, application to a specific ornamental plant in one county. In this situation, only the population potentially affected, (i.e., living in the county), should be considered in the risk assessment. The rest of the population would be handled in a separate aggregate exposure and risk assessment.

A pesticide with a broader use pattern may require a drinking water exposure assessment that includes multiple counties, states, even a geographic region. Such an assessment could be conducted by combining residue data from various drinking water sources, if the data are judged to be sufficiently similar through appropriate statistical tests. However, pesticide use usually impacts different drinking water sources to different degrees. This should be taken into account in the exposure assessment. For example, a particularly vulnerable water source (community water system) would be suitable for use in estimating the potential drinking water exposure for individuals who drink from that community water system, but should not be the basis for an exposure assessment for individuals living nearby, but drinking from another, less vulnerable source of drinking water. In these situations where residue data from several drinking water sources may be combined into one distribution of residue data, it is desirable to know the population associated with any specific drinking water source included in the exposure assessment. Knowing the size of the population served by a specific drinking water source allows for population-weighted exposure assessments. A population-weighted exposure assessment accounts for the probability that a specific portion of the population considered in the assessment may be more highly exposed than the majority of the population considered. Aggregate risk assessment procedures are flexible enough to accommodate these situations.

3. Residential Pathway and Aggregation

Assessing potential aggregate exposure to pesticides resulting from applications made in and around the home and public places such as playgrounds and playing fields, is also influenced by temporal, spatial, and demographic considerations. In addition, age and regional characteristics play a significant role when addressing an individual's residential exposure in an aggregate exposure assessment.

In general, a decision to use a pesticide depends on a perceived need for control of a certain pest or group of pests. For example, those desiring a weed free lawn are inclined to use an herbicide at different times of the year based on when weed seeds are germinating or shortly after they have emerged. An individual makes a decision to treat a lawn oneself or to hire a professional lawn care operator (LCO). Urban houses may receive pesticide treatment for chronic pests such as cockroaches on a routine basis. Exposure of young children in any of these environments may be higher than adults because of their unique behavior (non-dietary ingestion, i.e., hand-to-mouth), increased activity or greater contact with the floor where pesticide applications may have been made. An assessor should attempt to make a connection between these residential pesticide use preferences and a particular type of individual, based in data.

Temporal considerations can be identified by focusing on the pest to be treated and whether the application has been made by the resident himself or a professional applicator. Weed control on lawns using broadcast applications is typically performed in the spring to control germinating or newly emerging weeds. Insects such as billbugs or sod webworms appear in lawns as the season progresses. Summer weed control tends to be accomplished by the use of spot applications either made by the resident using a hand held sprayer to specific weeds or along patio borders. Professional applicators normally treat weeds during the summer on an as needed basis while making routine fertilizer treatments. Most lawn care operators (LCO's) have an additional trigger on their spray wands to activate the herbicide spray when they run into a weedy spot during the fertilizer treatment. Residents typically have poor knowledge of turf diseases and thus are less likely to use fungicides while professional lawn services are likely to anticipate disease conditions and make appropriate treatments. Temporal consideration regarding the use of LCO's and the time of the week of application need to be considered. Typically, treatments are likely to be made by a professional during the work week and by the resident on the weekend. An assessor should link the probability of professional or self-applied residential pesticide with an individual in an aggregate assessment, based in available data.

Spatial (geographic) considerations can also be identified by focusing on the site/pest considerations such as fire ants on lawns in the South. The use of a pesticide may be limited to cool season grasses which are primarily grown in the north and Midwest. Home gardens in the humid Southeast may require more fungicide treatments than gardens in California. For example, the periodic cicada is a problem in the Northeast, yet does not occur in the Pacific Northwest. Spatial considerations can be made for the characteristics (*e.g.*, location of residence) for each individual in the population.

Demographic considerations are important for adequate characterization of individuals in the

population. For example, urban poor and rural poor may have different pesticide usage patterns based on likelihood of having a vegetable garden or increased domestic pest pressure due to urban multifamily dwelling living environment. Low income residents in suburban areas may be less likely to hire lawn services than other suburbanites. Those who own homes may be more likely to hire lawn services than those who rent. These demographic considerations can also be considered for each individual in the population.

Age/gender/pathway considerations play a role in aggregate assessments related to the behavior of the individual. Young children may be exposed to more pesticide residues because of hand-to-mouth activity (non-dietary ingestion). Some national surveys of home and garden pesticide usage suggest that more males than females treat lawns while females are more likely to treat the interior of the house. These considerations will aid in developing reasonable and realistic aggregate exposure and risk assessment scenarios.

IV. How to Perform Aggregate Exposure and Risk Assessments

The Revised Guidance and steps in performing aggregate exposure and risk assessments are not meant to be comprehensive or to be interpreted as the required approach. EPA will evaluate any and all methods or models developed to assess aggregate exposure. However, the framework, principles, and the contents of the steps should be strongly considered by any aggregate exposure and risk assessor.

A. Distinctions in Revised Approach

The following section describes EPA's proposed practices and principles for addressing aggregate exposure and risk assessment under FQPA. These practices update and revise the *Interim Aggregate Exposure and Risk Assessment Guidelines* discussed above. Prior to introducing the Ten Steps to consider in implementing the revised aggregate exposure and risk assessment methods, it is important to make two additional distinctions between the *Interim* guidelines for aggregate assessment and the revised guidelines. One is that aggregate exposure assessments built individual-by-individual, culminating in a total exposure to the population, may allow for probabilistic treatment of data incorporating all pathways of exposure, *i.e.*, food, drinking water, and residential. Following is the discussion of how to combine the three pathways of exposure in an aggregate assessment using distributional data mentioned in Section II. The other distinction is that the revised aggregate guidelines methods may allow for more detailed use of toxicological factors of interest. These two new elements are discussed below.

The way in which distributional data sets from all three exposure pathways (and routes) for individuals in the population are combined within one aggregate assessment may be different utilizing the revised approach to aggregate assessment. The appropriate means of combining probabilistic exposure estimates from food, drinking water, and residential exposure involves combining exposures for a single chemical from all pathways for each individual (separately) in the population. In this way, the aggregate exposures in a population of individuals (*e.g.*, U.S.

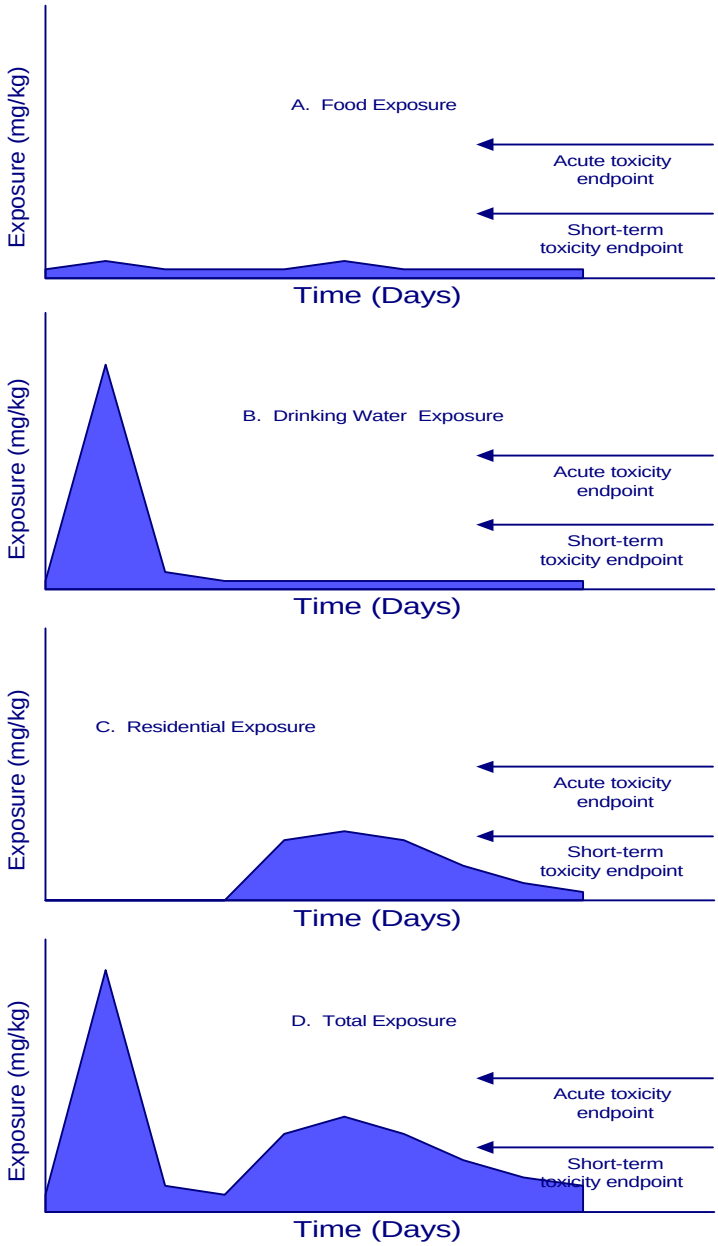
population or children ages 1-6 years old) is a collection (distribution) of exposures of all the individuals in the population. The individual's aggregate exposure distribution is defined by applying the key concepts presented in Section III.

For example, it is not appropriate to derive separate distributions of exposed individuals for each pathway of potential exposure, and to then merely sum exposure from each pathway to derive a distribution of aggregate exposure of a population of individuals. The assessor should identify interconnected individual-specific pathway exposure scenarios that are reasonable and supported by data. In essence, the incorrect approach would place three sets of individuals (or three different populations), which are not connected through logical correlations and linkages of potential exposure, into one population aggregate exposure distribution. In this case, each "individual" would represent a series of illogical and incoherent set of exposures which would not occur in reality. Therefore, it is imperative to attempt to honor the temporal, spatial and demographic data available for each individual in the population when creating an aggregate assessment of population.

Aggregate exposure and risk will be assessed using probabilistic methods whenever possible. These methods will allow for more detailed use of toxicological data than today's methods. OPP selects multiple toxicological endpoints for pesticides to reflect a variety of time frames (acute, short term, intermediate term, and chronic) and routes of exposure (oral, dermal, and inhalation). The endpoint selected for use in evaluating risk from a variety of exposure scenarios should be consistent with respect to the toxicological factors and use pattern time frames of interest as well as personal/individual characteristics of each individual in the population. When an aggregate assessment is conducted using a calendar-based approach, the results of the assessment should be presented in a manner similar to Figure 3. In Figure 3, the magnitude of daily exposures indicated on the *y* axis. The change in magnitude of exposure is plotted with time on the *x* axis. In these examples, the potential for an exposure value which exceeds the reference dose (RfD) is determined by comparing the magnitude of daily exposure to a toxicological endpoint such as an acute or short term RfD. Determination of which endpoint should be used for comparison is based upon the duration and route of the exposure.

Figure 3. Pathway specific exposure peaks.

Low-level constant exposure



The previous example (Figure 3) demonstrates the relationship between duration of exposure and the toxicology endpoint. Figure 3 displays the three pathway-specific exposure distributions (food, drinking water, and residential) and the total exposure distribution when an acute endpoint is selected. The noticeable 'spike' in the second and fourth bar can be considered a change in drinking water exposure. In these bars, there is an increased exposure to the compound of interest, but the increase persists for only one or two days. The appropriate comparison would be to the acute RfD which is exceeded in both the second and fourth bar in Figure 3. Comparison to the short-term endpoint would be inappropriate because the duration of the increased exposure relative to background exposure is of insufficient duration according to the definition of short-term exposure of 1-7 days. The opposite case occurs in the Residential Exposure example, the third bar in Figure 3. Here, the increased exposure occurs for several days in a row, during which time the short term RfD is exceeded. Comparison to the acute RfD would be less appropriate in this case according to the definition of acute exposure which is 1-day or less. The final example is an illustration of the possible results from an aggregate assessment combining all three pathways of exposure. Here, the proximate relationship between the two episodic exposures and the over layering of the background food exposure means that a number of time-based toxicological criteria (*e.g.*, acute RfD, short-term RfD) can be calculated. In this case, a potential concern for acute exposure exists from drinking water exposure (during which time the acute RfD is clearly exceeded). The concern for the short term exposure from the residential scenario also remains.

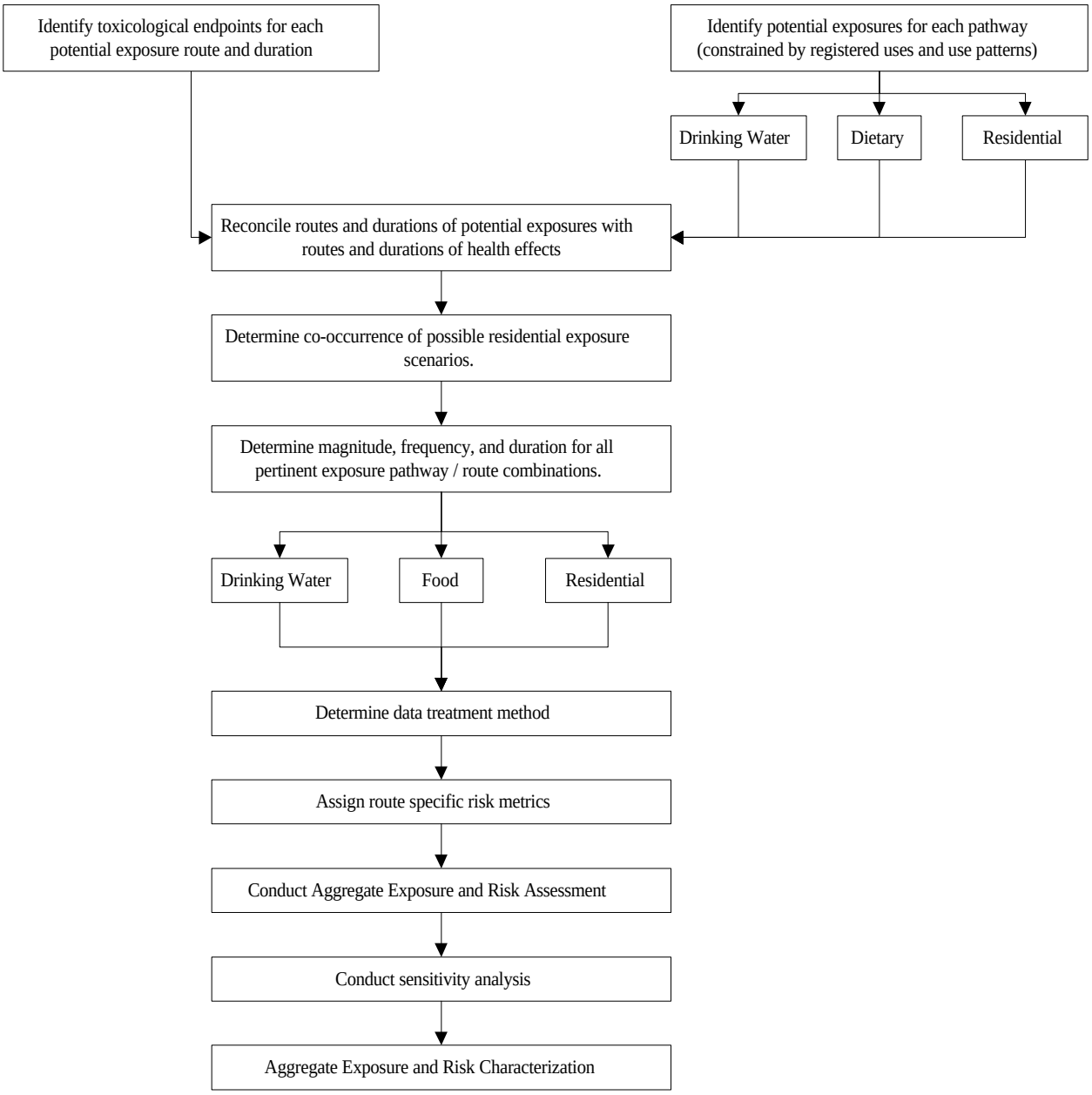
However, an added complexity is introduced because a constant exposure to the compound continues in the time interval between the two episodic exposures. This intervening exposure represents the combination of the background food and water exposures and is roughly half the short-term RfD. The short term RfD is clearly exceeded during the acute drinking water event. If the short term effect of concern is not clearly reversible within the one day between the drinking water exposure and the introduction of the residential exposure, this entire series of exposure will be treated as a single, continuous exposure for the purposes of risk assessment. If the effect of concern is reversible within the one-day time frame, the exposures can be treated as discrete events. Through aggregate exposure assessment techniques an assessor may be able to examine in more detail the relationship between the duration of exposure to an individual in a population and the toxicologically significant exposure duration in which an adverse effect may occur. This helps to create a more realistic sense of exposure to individuals in a population.

Aggregate exposure and risk can also be evaluated by considering the distribution of aggregated total exposures, much as is currently done for acute dietary assessments. The range of exposures and their relationship to the critical toxicity endpoints would provide a profile of possible exposures of concern. In particular, the tails of the exposure distribution would contain individuals subjected to a number of high exposures, probably from a variety of co-occurring exposure pathways. The origin of exposure to these individuals should be evaluated to the extent possible to determine if a particular pathways should be considered for mitigation. The tails of the distribution can also be evaluated to determine if it is comprised mainly of individuals representing a definable highly-exposed sub-population in which case further investigation/ analysis would be warranted. A qualitative evaluation of likely exposed sub-populations should also be made to

determine if any sub-population of concern is likely to experience unusually high exposure based upon lifestyle considerations. Isolation of the subgroup may provide an indication of possible mitigation strategies to reduce exposure.

The following are guidelines for assessing aggregate exposure and risk to individuals in a population. See Figure 4 for an overview of the sequence of steps to consider in an aggregate exposure and risk assessment.

Figure 4: Steps in Performing Aggregate Exposure and Risk Assessment



B. The Ten Steps

1. Identify toxicological endpoints (i.e., effect, dose and duration) for each potential exposure route (i.e., oral, dermal, inhalation) and exposure duration (short term, intermediate term, and long term). The appropriate exposure duration would be selected and identified by consideration of the timing of health effects (day, week, chronic, or an intermediate interval), the duration of the health effect (i.e., the reversibility of the effect) and the time to onset of the health effect.

An initial step in performing an aggregate risk assessment is to identify the toxicological endpoints of concern for a particular pesticide active ingredient. Frequently, there may be more than one toxicological endpoint for a single chemical. If the toxicological effects via different routes of exposure are not the same, then those exposure scenarios should not be combined. More than one aggregate exposure and risk assessment can be performed, if necessary, evaluating each endpoint separately. Factors to be considered in evaluating a toxicological endpoint include the type of effect, the dose level, the duration of the effect, and the time to onset of the effect. All these considerations will be included in the identification of appropriate exposure scenarios via all pathways (*i.e.*, food, drinking water, and residential) in the analysis of aggregate exposure and risk.

An additional consideration is the potential difference in the toxicity of a pesticide resulting from different routes of exposure. The differences may result from pharmacokinetic factors including rate and degree of absorption, distribution, and potential differences in metabolism. Materials absorbed through the skin may be partially metabolized as they enter the skin. Alternatively, some pesticides may require activation by the liver. The liver may be bypassed when chemicals are absorbed through the lung and skin and therefore exposure via these routes may not result in bioactivation in the liver. The toxicity endpoint may also vary in treatment in the risk assessment depending upon the assumptions made about its interaction with the body. For instance, considerations of threshold may be important for non-cancer endpoints. Although low-dose linearity is typically assumed for cancer, mechanistic research is increasingly providing support for non-linear dose response for certain cancer effects (*e.g.*, thyroid carcinogenicity via perturbation of thyroid-pituitary axis).

For example, if a particular pesticide active ingredient elicits an effect only following oral administration, and no effects are seen via the inhalation or dermal routes, only those exposure scenarios which reflect the oral route of exposure will be included in the analysis of this toxicological endpoint. Specifically, in this example, only the food pathway, any oral pathway residential exposure scenarios listed in the Residential SOPs, and the drinking water exposure scenarios would be evaluated in the assessment of aggregate exposure and risk. The timing of the health effect via an oral route of exposure would depend upon the timing of the effect seen in the animal studies. If there is no effect seen at the acute dose level, but there is an effect in the long term (1-year dog study), only the long-term exposure scenario would be evaluated.

Toxicological effects which occur at different dose levels via different routes of exposure should be combined within an aggregate exposure and risk assessment. A conversion to a common risk metric may be required, however, to adequately combine the routes of exposure. Steps to combining pathways of exposure and things to consider while developing route specific exposure scenarios, and combining exposure scenarios, are provided below.

The importance of the time to onset of toxicological effect can be seen in Figure 4 above. While a single pathway-specific exposure scenario for an individual or group of individuals in the population may not result in a duration of exposure which equals or surpasses the time to onset of effect for a specific chemical, a combination of exposure scenarios for an individual or group of individuals in the population may exceed the time to onset of effect. Through the development of a coherent and logical "individual" in the aggregate exposure population, the time to onset of effect can be adequately compared to the exposure duration for a more realistic aggregate exposure and risk assessment.

The hazard identification step in the development of the aggregate risk assessment process should proceed in parallel with the development of appropriate exposure scenarios. The toxicity endpoint should match the temporal and spatial (regional) characteristics of the exposure scenarios selected as requiring inclusion in the assessment. However, the selection of exposure scenarios of concern will also be impacted by the toxicity profile of the pesticide, especially factors relating to the time of onset of effects and duration of effects or period of reversibility. Neither aspect of the assessment outweighs the other. Rather they should be evaluated in concert to ensure that all appropriate scenarios are accounted for and that all toxicity endpoints of concern are addressed.

> *2. Identify the potential exposures (including duration and route) for each pathway for each individual in the defined population. The universe of potential exposure scenarios should be constructed by first identifying the registered uses and the use patterns for the chemical.*

The universe of potential exposures to an individual to be considered in an assessment is a function of the amount of data available to an assessor, the level of refinement desired, the degree of variability and uncertainty an assessor wishes to assess and/or eliminate, and other factors related to the possible modeling tools available to the assessment. Ideally, the universe of potential exposures is representative of the total population and the sub-groups of potential concern in a specific assessment. At minimum, an assessment would fully utilize all data records available in the CSFII and all residential SOP scenarios could be investigated through creation of an "individual." Whereas EPA is not defining any particular methodology to perform aggregate exposure and risk assessment, EPA is also not defining any number of potential exposure scenarios or individuals to include in the assessment. Depending on the registered uses and use patterns for the chemical, this parameter may range from a few individuals and/or scenarios to many hundreds or thousands.

In addition to considering the toxicological effect, dose level, duration of effect and timing of effect, the analyst should also consider all registered uses and use patterns of the pesticide active ingredient in developing logical aggregate exposure scenarios via all relevant routes of exposure. Evaluating all registered use patterns will enable the analyst to determine for the food pathway, for example, which crops and crop groups should be included in the analysis; for the residential pathway, which uses are registered for the chemical and, therefore, which residential application scenarios should be included in the analysis; and, a review of registered uses and use patterns will allow the analyst to determine not only if a probability of drinking water contamination should be evaluated, but also allow the analyst to perform localized drinking water assessments, if data are available. Of the seemingly limitless combinations of food, drinking water, and residential pathway scenarios which could be developed in an aggregate exposure assessment, a review of the toxicologically appropriate constraints (*e.g.*, the duration of effect) and the registered uses and use patterns would likely significantly limit the number of aggregate exposure scenarios to be evaluated.

Because of the complexity introduced into the risk assessment process by the multitude of potential exposure scenarios, the identification of the potential aggregate exposure scenarios to be included in the assessment should be preceded by the bounding of all exposure scenarios. This is an important step in determining the scope of the assessment. This bounding process will greatly simplify the data preparation and calculation phases, but will also make the risk characterization process more transparent and useful by permitting the attention of the risk manager to be focused on the more important aspects of the assessment. A first step in the bounding process is the evaluation of the relative contribution/importance of the various routes and pathways that may be of concern in the final risk estimate. Where a particular pathway will likely contribute less than 1.0% of the total exposure in the most refined analysis performed, it should be noted in the risk assessment as extant but not included in the quantitative risk assessment. Similarly, if specific uses make negligible contributions to the risk assessment because of limited use or low consumption, or the toxicity by a particular route is low, the uses or routes should be noted in the risk assessment, but not included in the quantitative risk assessment. The rationale for exclusion from the quantitative risk assessment should be explained in each case.

A negligible contribution from a pathway or route can be demonstrated by conducting a bounding estimate for a given pathway. A bounding estimate is one in which several conservative assumptions are combined to provide an estimate of exposure unlikely to be exceeded in actual occurrence. An example of a bounding estimate for food exposure is a Tier 1 or 2 acute assessment in which the entire crop is assumed to be treated and residues are assumed to be present at tolerance level. The actual exposure in the diet is unlikely to exceed this level and in most cases is anticipated to be much lower. For residential exposure assessments, use of the assumptions defined in the Draft Residential SOPs (US EPA, 1997a) with no adjustment for chemical specific data or other better data would provide a reasonable bounding estimate. The use of surface water and groundwater concentrations generated by water quality models currently used in OPP (GENEEC, PRZM/EXAMS, and SCI-GROW) would provide a bounding estimate for comparison to a DWLOC for the drinking water portion of the assessment.

Examples of negligible exposure scenarios which could be excluded include the following: the absence of residential uses for residential assessments, child-proof packaging such as bait boxes used in a residential setting, registrations only on minor use crops, low acreage applications; and for water, pesticides with low leaching or runoff potential or use patterns unlikely to impact drinking water resources. Although, these factors alone cannot be used to rule out a pesticide's potential impact on drinking water, arguments of negligible risk based upon toxicity considerations could include no evidence of adverse effect in adequately performed toxicity studies by a particular route or quantitatively different toxicity among routes such that one route would be likely to dominate the risk assessment. If other bases for arguing that a scenario represents negligible exposure or risk can be provided, they will be considered on a case-by-case basis. Unnecessary complexity (i.e.,-modeling parameters with little impact on the assessment) should be avoided. A sensitivity analysis will provide insight into the significance of any parameter in the risk assessment (See #9 of this section). In some instances, defaults or point estimates may be an adequate level of refinement.

> *3. Reconcile the routes and duration of potential exposures with the routes and durations of the health effects. By matching exposures (by route and duration) with the toxicological endpoints (by route and duration) and then conducting an aggregate risk assessment on the matches only when the integrity of the individual relationship between the endpoint, route, and duration is maintained.*

Determining which routes (*i.e.*, ingestion, inhalation, and dermal) and pathways (*i.e.*, food, drinking water, and residential) are to be aggregated is a key decision in the development of an aggregate exposure assessment. Two general factors control this decision process -- the biologically relevant dose and the potential exposure pattern of the active ingredient. The exposed individual's dose should be matched against a relevant toxicological dose in terms of route, duration, and effect. For example, evaluating the application of a lawn treatment in December in Maine may be allowable by the data, but defies logic. No such application is likely to take place and, thus, does not merit inclusion in the risk assessment. The careful evaluation of all route- specific exposure scenarios based on timing of effect and other toxicologically relevant characteristics as well as the registered uses and use patterns, and then the matching of those scenarios based on data that support the combinations further assures the integrity of the aggregate exposure scenarios.

These assumptions for individuals may be extended to populations and sub-populations of concern by constructing distributions of individual doses. Assumptions should reflect time (duration, frequency, seasonality); location (place and type of residence, urbanization, drinking water sources, region); and demographics (age, gender, reproductive status, ethnicity). All 'linkages' of time, space and demographic characteristics should be made using supporting data.

To further illustrate this basic assumption, consider two individuals -- a man living in a single-family home in rural central Florida and a woman living in an apartment in Chicago. The individual in Florida depends on a private well for drinking water, performs his own lawn care,

treats his home several times a year for roaches, has a private swimming pool, and eats locally produced food for nine months a year. The individual in Chicago depends on municipal drinking water, does not have a private lawn or swimming pool, lives in an apartment with monthly scheduled pest control service, and eats locally produced food only in the late summer. Based solely on time, place, and demographics it is likely that these two individuals have significantly different potential exposures to a given pesticide. After defining the toxicological endpoint (effect) and route of concern, the assessor should decide upon the appropriate set of residential, food and drinking water exposure assumptions for combining these risk scenarios. The decisions concerning which residential scenarios should be considered in aggregate risk assessments should be made using the scenarios in the Residential SOPs as a basis for primary selection.

4. Determine which of the possible residential exposure scenarios occur together (i.e., co-occur within a given time frame) and which occur independently.

Within the residential exposure pathway there are numerous exposure scenarios, via all routes of exposure. Some of those events might be linked or correlated such that the use of one affects the likelihood of use of another. For example, it is true that the use of one product may generally preclude the use of another and that a homeowner is unlikely to use more than one type of roach repellant to treat a given roach infestation problem. On the other hand, the use of one home pesticide product may indicate the use of another. For example, it is not unusual for a person performing conventional treatment of flea infestation to concomitantly treat the pet with a type of dog-dip and spray for the fleas in the home, so as to completely eliminate the problem and lessen the chance for reoccurrence. These types of co-dependencies and inter-relationships should be evaluated fully so as to properly discount unlikely and unrealistic combinations of residential exposure scenarios while at the same time appropriately accounting for correlated or linked uses. Marketing data may be available to aid in evaluating these dependencies**.**

An example of a scenario in which multiple products are likely to be used is the flea infestation scenario. When a flea infestation occurs, a pet owner is likely to spray the pet, treat the carpet and bomb the residence in order to alleviate the problem and reduce the likelihood of recurrence. These three patterns of use would be viewed as linked for the purposes of aggregate risk assessment. Where adequate data are available, the residential component of the exposure should be included in the aggregate assessment through a series of probability distributions to combine the various potential residential scenarios with the food and drinking water portions of the assessment. A presentation of OPP's guidance on preparation and submission of the residential portion of the exposure assessment can be found in the *Guidelines for Submitting Probabilistic Analysis to the Office of Pesticide Programs* (1998c). Information in this document is fully consistent with the preparation of aggregate risk assessments.

5. Determine magnitude (i.e., exposure concentration), frequency, and duration of exposure (i.e., contact) for all pertinent exposure combinations.

For all relevant exposure routes and pathways identified in the previous steps, the magnitude of

exposure and risk should be calculated for each pathway/route separately, then brought together as a total risk value. The pathways/routes to be considered are food/oral; drinking water/oral; and, residential/oral, dermal, inhalation. Sections II and III of this document describes the general considerations in determining the magnitude of exposure for these pathways. The magnitude of exposure may be determined through use of residue data, such as for the food pathway. In the absence of residue data, exposure estimates may be based on modeled data and assumptions made in the absence of actual data, such as for the residential and drinking water pathways. The following section describes some of the specific points to consider when bringing together these three pathways/routes of exposure.

In order to bring together exposure pathways (food, drinking water, and residential) to chemicals used as pesticides, a number of steps need to be taken. Of particular importance is the allowance for temporal and spatial considerations with regard to likely overlapping of exposure events from a pesticide because of multiple sources of exposure. Temporal issues include those relating to seasonal variation within an exposure scenario. For example, certain types of behaviors (*e.g.*, lawn care) as stated earlier, are unlikely to occur in the cold winter months in the northern part of the country. Similarly, contamination of water by corn herbicides is most likely to occur in the spring but is less likely to occur in the winter months. Another temporal aspect which should be considered is the frequency of and time interval between, exposure events. If a home owner fumigates a house today, it is unlikely that fumigation would be repeated tomorrow. However, residual exposure may continue for the next several days following fumigation although at a reduced level. Spatial considerations include at the macro level the region of the country and climatic differences that may be anticipated. These differences include allowances for the seasonal differences in temperature that occur depending upon the region. In this example, the impact of a region coincides with temporal considerations. For example, impacts of winter on use patterns for pesticides would be very different in Maine than in Florida. Another type of spatial consideration would be the identification of rural versus an urban setting. A private well as primary water source is much more likely to be associated with a rural setting than an urban setting. Similarly, regional production of fresh market produce may impact the need for a regional dietary assessment especially during peak harvest season. The following sections describes in detail the steps to consider when determining aggregate exposure and risk.

6. Determine most appropriate technique (deterministic or probabilistic) for incorporating data into exposure algorithms.

Once input data are collected for exposure variables of interest, several techniques are available for representing these variables. EPA has traditionally used a deterministic approach to generate a single estimate of exposure and risk based on expressing all input variables in the exposure algorithm as single values (point estimates). Alternatively, one can use probabilistic techniques to more fully incorporate available information taking into account the range of possible values that an input variable could take, and weighting these values by their probability of occurrence. Probabilistic techniques acceptable to EPA are discussed in a recently developed guidance (US EPA, 1998d). EPA anticipates that a probabilistic approach to exposure assessment via all

pathways will be used in the future.

7. Determine the appropriate risk metric to be used in analysis and calculating aggregate exposure and risk.

There are several methods of measuring and aggregating risk for single chemical, multi-route, multi-source assessments. The following three methods are among those used by the Agency. Two aggregation methods were developed by OPP – the Total MOE and the Aggregate Risk Index – which are easy to use and do not require route extrapolations (Whalan and Pettigrew 1998). A third method – The Hazard Index – is the reciprocal of the Aggregate Risk Index and is used for Superfund risk assessments (USEPA, 1989); it is being considered for use in OPP. The selection among these methods depends, in part, on the required use of uncertainty factors.

Currently, risk assessments in OPP are based on the Margin-of-Exposure (MOE) concept. As a rule, risk increases as the MOE decreases. Each MOE is compared against an Uncertainty Factor (UF) which serves as a standard when ascertaining whether a given hazard is acceptable.

Total MOE (MOE_T) Method:

The following aggregation equation has been used since April 1996 to aggregate "unit-less" MOEs into a **Total MOE** (**MOE_T**). This concept was presented to, and endorsed by, FIFRA's Science Advisory Panel (McConnell *et al.*, 1997):

Equation 1

$$MOE_T = \frac{1}{\frac{1}{MOE_1} + \frac{1}{MOE_2} + \ldots + \frac{1}{MOE_n}}$$

All MOEs should be compared against the same Uncertainty Factor (UF - typically 100 for interspecies extrapolation and intraspecies variability), as in this example:

Oral	MOE = **100**	UF = 100
Dermal	MOE = **200**	UF = 100
Inhalation	MOE = **70**	UF = 100

Equation 2

$$MOE_T = \frac{1}{\frac{1}{100_O} + \frac{1}{200_D} + \frac{1}{70_I}} = 34.1$$

The MOE_T is always lower than the lowest MOE. The MOE_T decreases with each additional MOE in the equation because each additional exposure increases the hazard. The lowest MOE (the inhalation MOE of 70 in this example) has the most influence on the MOE_T. The MOE_T of 34.1 is of concern because it is less than the acceptable UF of 100. A major deficiency of this method is that it cannot accommodate dissimilar UFs (i.e., UFs other than 100).

Ideally, route-specific MOEs for each route of exposure should be aggregated. When inadequate toxicity data make this approach impossible, data from another route can be substituted although this introduces some degree of error. For example, an inhalation MOE can be calculated by using an oral NOAEL that has been extrapolated to an "equivalent" inhalation NOAEL. Error results from using an extrapolation method that does not account for pharmacokinetic differences between the routes, and from assuming that the route with no data will have the same toxic signs as the well characterized route.

Aggregate Risk Index (ARI) Method:

The Aggregate Risk Index (ARI) was devised as a way to aggregate MOEs that have dissimilar UFs. Because of its versatility, it supersedes the Total MOE method, and has been used in OPP since February 1998. MOEs for each route of concern are compared against UFs which reflect the nature, source, and quality of the data, and the FQPA mandate to protect susceptible infants and children. This can result in a variety of UFs such as these:

	Oral	**Dermal**	**Inhalation**
MOE:	300	100	1000
UF:	1000	100	300

MOEs can only be combined if they have a common UF. If the MOE/UF ratios for each route are treated as fractions (as shown above), they can be adjusted to a common denominator of 1. This is accomplished by dividing each MOE by its UF to yield a **Risk Index** (**RI**):

	Oral	**Dermal**	**Inhalation**
RI:	0.30	1.0	3.3

The RIs can then be combined to yield an **Aggregate Risk Index (ARI)**:

Equation 3

$$ARI = \frac{1}{\frac{1}{RI_1} + \frac{1}{RI_2} + \ldots + \frac{1}{RI_n}}$$

Equation 4

$$ARI = \frac{1}{\frac{1}{0.30_O} + \frac{1}{1.0_D} + \frac{1}{3.3_I}} = 0.22$$

RIs and ARIs are always compared against 1. This allows for direct comparisons between routes and between chemicals. As a general rule, an RI or ARI ≥ 1 is of little concern, but an RI or ARI <1 suggests a risk of concern. In this example, the ARI (0.22) suggests a risk of concern because it is <1. The oral exposure has the lowest RI (0.30), so it is the major route of concern.

The Aggregate Risk Index (ARI) is an extension of the MOE concept. As with the MOE, risk increases as the RI or ARI decreases. The ARI method automatically considers each route's potency when route-specific NOAELs are used. The following equation is a simplified way of calculating a chemical's ARI in a single step:

Equation 5

$$ARI = \frac{1}{\frac{UF_1}{MOE_1} + \frac{UF_2}{MOE_2} + \ldots + \frac{UF_n}{MOE_n}}$$

Oral hazards are usually expressed as the "Percent of RfD" rather than as an MOE. Because the UF for the oral route is used to define the oral RfD, the percent of RfD (expressed as a decimal) can be put directly into the equation (assume oral exposure is 80% of the RfD, i.e. 0.8):

Equation 6

$$ARI = \frac{1}{\%\ RfD_O + \frac{UF_D}{MOE_D} + \frac{UF_I}{MOE_I}}$$

Equation 7

$$ARI = \frac{1}{0.8_O + \frac{100_D}{100_D} + \frac{300_I}{1000_I}} = 0.48$$

Percentages of reference doses (RfDs) and reference concentrations (RfCs) for all routes may also be aggregated:

Equation 8

$$ARI = \frac{1}{\%\ RfD_O + \%\ RfD_D + \%\ RfC_I}$$

Hazard Index (HI) Method:

The **Hazard Index** (**HI**) is another aggregation method used by other parts of the Agency. The HI is an aggregation of individual **Hazard Quotients** (**HQ**) for each route of exposure. The HQ, which is a percent of RfD or percent of RfC, is calculated as follows:

Equation 9

$$HQ = \frac{Exposure\ (mg/kg)}{RfD\ (mg/kg)} \qquad HQ = \frac{Exposure\ (mg/L)}{RfC\ (mg/L)}$$

This method requires that an oral RfD, dermal RfD, and/or inhalation RfC be defined for each route of concern (the RfD and RfC are calculated by dividing a NOAEL by a summation of UFs). HQs (*i.e.*, percent of the reference dose (RfD) or reference concentration (RfC)) for each route of concern can be aggregated into an HI:

Equation 10

$$HI_{pathway} = HQ_O + HQ_D + HQ_I$$

Equation 11

$$HI_{Total} = HI_{Residential} + HI_{Dietary} + HI_{Drinking\ Water}$$

Risk <u>increases</u> with increasing values of HQ or HI. Generally, an HQ or HI ≤ 1 is of little concern, but an HQ or HI >1 suggests a risk of concern. The ARI is the reciprocal of the HI (compare Equations 8 and 10).

> *8. Conduct analysis to determine the magnitude of exposure and risk for each pertinent exposure pathway. Aggregate as appropriate, exposure and risk by route, then by pathway, into a total exposure and risk from all routes and pathways to each individual in the population and then to the population as a whole. Several aggregate exposure and risk assessments may be required for a single active ingredient.*

In review, developing realistic, aggregate exposure and risk assessments requires that the appropriate temporal, spatial, and demographic exposure factors be correctly assigned and consistently maintained throughout the analysis. Specific considerations should include:

- Time (duration, frequency, and seasonality of exposure; seasonally-based pesticide residues in food; frequency of residential pest control which reflects housing location and type);
- Place (location and type of home); watershed (size of drinking water facility) or aquifer characteristics (confined or unconfined); region (regionally specific drinking water concentrations of the pesticide being considered); and
- Demographics (age; gender; gender- and age-specific body weights; reproductive status; ethnicity; personal preferences, behaviors, and characteristics).

All ‘linkages’ of time, space and demographic characteristics should be made using supporting

data. Aggregate exposure and risk assessment are first completed for individuals, who are then combined to develop distributions of aggregate exposure to sub-populations and populations.

Exposures and resulting risks should be combined for all routes that result in qualitatively similar toxic effects. If the effects of concern are not qualitatively the same, then the exposures should not be combined. Individual exposure and risk assessments should also be conducted for each potential route and source of exposure. Individual exposure assessments will provide the basis for developing risk mitigation strategies in the event that an unacceptable aggregate risk is indicated.

The choice of input distribution should always be based on all relevant information (both qualitative and quantitative) available for input. The selection of a distributional form should consider the quality and quantity of the information in the database, and should address broad questions such as the mechanistic basis for choosing a distributional form, the discrete or continuous nature of the variable, and whether the variable is bounded or unbounded. In all cases, input values expressed as a distribution should be fully described. (US EPA, 1998c)

Not all input values need, or should, be expressed as a mathematically-modeled distribution, and probabilistic techniques should not be used only on those pathways and exposure patterns which significantly influence the final risk estimate. If an input variable does not significantly affect an exposure estimate regardless of its distribution, then its use in a probability distribution represents marginal value added. (US EPA, 1998c)

> *9. Conduct sensitivity analysis to identify the "driver" or source(s) of risk for each route. Identify scenario(s) of concern, such as highly exposed subpopulations by sources*.

After performing an aggregate exposure and risk assessment, it may be helpful to also conduct sensitivity analysis to ascertain the route, pathway, exposure scenario, commodity, or other element of the analysis, which contributes the highest amount to total exposure and risk. Those routes and pathways with the lowest risk index (RI) or the greatest hazard quotient (HQ) pose the greatest risk, and are the most likely candidates for risk mitigation. Sensitivity analyses can be performed to learn how changes to input assumptions affect changes in the result. Sensitivity analysis in aggregate exposure and risk assessment is performed by examining areas of high exposure and defining the differences in total exposure and risk without those exposure contributors. For example, in food exposure assessment, commodities with the most extensive use patterns, greatest consumption reported, and highest magnitude of residue data are likely to contribute the largest overall exposure for the food pathway. The inclusion/exclusion of this type of commodity from the analysis could provide valuable information as to the relative importance of this commodity to total exposure and risk.

A similar approach can be taken in examining the relative contribution of other routes of exposure or exposure pathways or other exposure scenarios within a pathway. For example, the analysis should focus upon which route of exposure contributes the largest portion of the total exposure, which residential scenario of the many that could be included in a single aggregate analysis is the

greatest contributor to exposure, or for the food exposure pathway, which commodity or commodities are the greatest contributors to the total food exposure value. With this knowledge, an aggregate exposure and risk assessor may be able to delineate ways in which total exposure and risk could be reduced, state for risk management purposes the pathway of exposure which represents the greatest proportion of the total risk, or decide where future data gathering efforts should be focused. Sensitivity analyses are particularly useful in deciding whether or not to elevate a pathway-specific analysis to the next level of data refinement and therefore consume more resources.

10. Aggregate exposure and risk characterization

The risk characterization process includes an integrative analysis followed by a risk characterization summary detailing the major results of the risk assessment. The integrative analysis brings together the assessments of hazard, dose response, and exposure to make risk estimates for the exposure scenarios of interest. The integrative analysis typically identifies the element of the aggregate analysis which most affects the exposure and risk conclusion for use in decision making. It is an appraisal of the science that supports the risk manager in making public health decisions. Risk characterization reports also indicate where the greatest opportunities for data or methodological improvements exist.

Risk characterization routinely includes the following points capturing the important items covered in hazard, dose response, and exposure characterization:

- primary conclusions about hazard, dose response, and exposure, including other plausible alternatives,
- nature of key supporting information and analytical methods,
- risk estimates and their attendant uncertainties, including use of key default assumptions when data are missing or uncertain,
- statement of the extent of extrapolation of risk estimates from observed data to exposure levels of interest (i.e., margin of exposure) and its implications for certainty or uncertainty in quantifying risk,
- significant strengths and limitations of the data and analyses, including any major peer reviewers' issues, and
- appropriate comparison with similar risk analyses, if appropriate, or common risks with which people may be familiar.

The risk characterization is a necessary part of generating any Agency report on aggregate risk, whether the report is preliminary to support allocation of resources toward further study or comprehensive to support regulatory decisions. In the former case, the detail and sophistication of the characterization are appropriately small in scale; in the latter case, appropriately extensive. Also, on the continuum from simple to more sophisticated assessments, default assumptions are used at almost every stage because the database is almost never complete. The use of defaults is predominant at screening stages and are used less as more data are gathered and incorporated.

The risk characterization should carefully delineate which issues in a particular assessment are most important.

The values supported by a risk characterization throughout the process are *transparency* in environmental decision-making, *clarity* in communication, *consistency* in core assumptions and science policies from case to case, and *reasonableness*. While it is appropriate to err on the side of protection of health and the environment in the face of scientific uncertainty, common sense and reasonable application of assumptions and policies are essential to avoid unrealistic estimates of risk (USEPA, 1995). Both integrative analyses and the risk characterization summary present an integrated and balanced picture of the analysis of the hazard, dose response, and exposure. The risk characterization should summarize of the evidence and results, and describe the quality of available data and the degree of confidence to be placed in the risk estimates. Important features include the constraints of available data and the state of knowledge, significant scientific issues, and significant science and science policy choices that were made when alternative interpretations of data existed (USEPA, 1995). Choices made about using default assumptions or data in the assessment are explicitly discussed in the course of analysis, and if a choice is a significant issue, it is highlighted in the summary.

C. Aggregate Assessment Reporting Requirements

The format for an aggregate risk assessment report should fully describe and document the ten steps for conducting an aggregate risk assessment as detailed in these guidelines. (Section IV. A. 1-10) In addition, information should be provided on: purpose and scope; inputs and assumptions; data sources; exposure algorithms and scenarios; and, definitions of defaults.

The purpose and scope of the assessment should be clearly stated in a "problem formulation" section that includes a full discussion of any highly exposed or highly susceptible sub-populations evaluated (e.g., children, the elderly). The questions the assessment attempts to answer are to be discussed and the assessment endpoints are to be well defined and supported. In addition, all inputs and assumptions for exposure and hazard portion of the assessment should be listed. Information for each input and output distribution is to be provided in the report. This includes tabular and graphical representations of distributions (e.g., probability density function and cumulative distribution function plots) that indicate the location of any point estimate of interest (*e.g.*, mean, median, high-end percentiles). The selection of distributions and whether distributions used for input parameters reflect re-sampling of empirical distribution functions or imputations should be explained and justified.

The sources for data used in an assessment should be clearly identified. Where these are studies that have previously been submitted, and/or reviewed by the Agency, identifying information such as petition number, reregistration submission, document number (MRID), or Agency review number should be provided, so the data points can be readily confirmed. Where data points have

been excluded from the probabilistic analysis, the exclusion should be identified and justified. Studies from which data are obtained should contain sufficient quality assurance/quality control of data to assure sample integrity during treatment, collection, transportation, storage, and analysis.

A discussion of the exposure algorithm and its appropriateness for the scenario and population under study is recommended. Names of models and software used to generate the analysis should be identified. Routes of exposure should be clearly defined. Sufficient information is to be provided to allow the results of the analysis to be independently reproduced. Moreover, the analyst should define all assumptions used and explain why they are reasonable. Assumptions that have a significant impact upon the results are to be documented and explained.

V. Future Data and Research Needs

The development of probabilistic aggregate risk assessment tools has greatly expanded the level of detail with which risk assessment can evaluate the variability and impact of pesticide use patterns on estimated risk. The importance of the rate of application of pesticides to foods and the distribution of pesticide use has been recognized as a potential area for refinement in estimating food exposure which has not always been included in the assessment process. The *Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs* includes a discussion of how use-related information can be better included in the risk assessment. That document also describes acceptable sources of data and how the data will be used. Other possible modifications to food assessments might include adjustment for residue levels in foods based upon differences in use patterns on fresh market and processed commodities or information concerning domestic vs. foreign production and treatment practices during different seasons.

A. Food Ingestion Pathway

In the area of food consumption, little data are available describing intra-individual variation in daily consumption patterns. Existing cross-sectional consumption data define inter-individual variation, but give little insight into intra-individual behavior over time. Longitudinal data exist for a few pockets of individuals in highly localized areas across the United States. More small surveys for a greater variety of sub-populations or a systematic subset nationwide would provide information needed to estimate the likely exposure of an individual to food borne pesticides over an extended period of time.

B. Drinking Water Pathway

For drinking water, in the short term, OPP is working to improve the current screening-level models used to estimate the concentration of pesticides in drinking water, particularly for surface water. Several approaches are being considered: 1) use of a crop area factor to take into account that 100 percent of a basin supporting a drinking water facility may not be cropped, and 2) modification of the pond scenario currently incorporated into OPP's screening-level water quality

models to simulate a small reservoir that is large enough to support a drinking water facility, and 3) development of a more refined screening model for groundwater. There is consensus among the water quality modeling community that a basin-scale water quality model linked to a Geographic Information System (GIS) to estimate concentrations of pesticides in drinking water with a moderate to high level of confidence, although not currently available, would improve the ability to predict concentrations of pesticides in drinking water. In addition, research to estimate of the extent to which various kinds of drinking water treatment remove pesticides from tap water would improve model estimates of pesticide concentrations in drinking water. The reader is referred to TRAC Science Policy Paper, "Estimating the Drinking Water Component of a Dietary Exposure Assessment 9/29/99 (Draft)," for further details on work in progress to meet future data and research needs.

There is the need to collect available data on pesticides in drinking water from state agencies for public health, environmental protection, water resources, etc., as well as to generate data on pesticides in drinking water from statistically-based surveys. For pesticides that are not screened-out by models and/or available monitoring data representing either drinking or non-drinking water supplies, data are needed on pesticide concentration distributions in drinking water for use in probabilistic aggregate exposure and risk assessments. Focused, targeted monitoring stratified across a variety of drinking water sources (vulnerable & typical) with known pesticide use for relevant pesticides are preferred. Data sets from most vulnerable drinking water sources (smaller facilities serving small populations) could be used with high confidence to bound the upper end of the distribution of pesticide concentrations in drinking water. Data sets from more typical drinking water sources (larger systems serving large populations) could be used with high confidence to bound the "middle" or central tendency of the distribution of pesticide concentrations in drinking water. For incorporating drinking water into acute and chronic aggregate exposure and risk assessments these are the most critical portions of the pesticide concentration distribution.

C. Residential Pathway

In the residential exposure pathway, the ability to precisely determine the likelihood of coincidental dietary and non-dietary exposure requires access to detailed use-related information. Use-related information includes details regarding the amount of pesticide applied per use, the frequency and timing of use events, and an estimate of the numbers and kinds of people making these applications. In addition, exposure assessors should be aware of applications made by consumers themselves and applications made by professional for hire services such as, pest control operators (PCO's) and professional lawn care operators (LCO's). Usage information sources include inferences from pesticide product labels and information provided by proprietary market research service firms such as Doane and Kline or government agencies. States such as California have databases of usage information which may not represent other regions and associations representing professional for hire services may also have usage information.

Frequency of use information, on a national scale, is available in the Agency's National Home and

Garden Pesticide Usage Survey (NHGPUS). However, this survey is 10 years old and focuses only on major use pesticides. In addition, this survey provides us very little information about post-application activities.

Increasingly, as pesticide registrants form data generating Task Forces in response to the FQPA, longitudinal surveys are being considered for use in residential exposure scenarios. These surveys are being designed to address usage, frequency of use, and other key information needed in an aggregate assessments such as demographic, geographic and seasonal variation.

VI. Limitations in Aggregate Exposure and Risk Assessments

There are limitations present in aggregate exposure and risk assessment whether the analysis utilizes deterministic or probabilistic treatment of data. Deterministic data used in an aggregate exposure and risk assessment can provide a conservative, "worst-case" estimate. However, as described by Cullen and Fry, because of the variability and uncertainty about exposure, the degree and direction of the conservatism associated with deterministic inputs and outputs is unknowable without detailed description of the specific exposure scenario and the exposure sources of consideration. Deterministic estimates based on conservative inputs provide no indication of the magnitude of uncertainty surrounding the quantities estimated and lend no insight into the key sources of underlying uncertainty. Analysts should be aware of the limitations surrounding the use of deterministic data sets and make these limitations known to the risk manager. (Cullen and Fry, p. 7)

The use of distributional data in a probabilistic aggregate exposure assessment also has some limitations. Probabilistic analysis enables a full characterization of the uncertainty and variability in the data set providing information about the range and likelihood of potential exposure. However, there are certainly cases for which probabilistic analysis is not the right choice. The main limitation of performing probabilistic aggregate exposure and risk assessments is that the assessor needs to consider all of the factors which enter into a discussion of when the use of the tool is desirable or not. After all, in many cases resource and data requirements to perform probabilistic analyses are substantial. The table below lists cases in which probabilistic analysis may and may not be useful.

<u>Cases in which Probabilistic Analysis May not be Useful</u>*

- When a screening level deterministic calculation indicates that exposures are negligible,
- When the cost of averting the exposure is smaller than the cost of probabilistic analysis,
- When safety is an immediate and urgent concern,
- When probabilities are so uncertain and/or indeterminate that detailed probabilistic judgements are impossible,
- When there is little variability or uncertainty in the analysis

Cases in which Probabilistic Analysis May be Useful*

- When the consequences of poor or biased exposure estimates are unacceptably high
- When a screening level, deterministic calculation indicates exposures of potential concern, but carries a level of uncertainty that does not warrant immediate expenditures on remediation
- When there is interest in the value of collecting additional information, such as when time and resources permit additional sampling, but questions remain about whether this will impact the quality of the decision to be made
- When uncertain information stems from multiple sources
- When significant equity issues are raised by sources of variability, such as when subpopulations face unusual exposures relative to those of the general population
- When assessing the potential benefits of targeting resources for various interventions, for example, when more than one strategy for remediation is available, but one would reduce exposure via the food chain while another would improve air quality
- When ranking or prioritizing exposures, exposure pathways, sites, or contaminants in important
- When the cost of remedial or intervention activity is high.

* Cullen and Frey, p.8

A. Food Ingestion Pathway: Limitations

Each of the exposure pathways described in this guidance has inherent uncertainties. However, the food exposure pathway is perhaps the most highly investigated pathway included in the aggregate exposure and risk rubric. While there are uncertainties in the food exposure analysis, the uncertainty decreases as higher tiers in food exposure analysis are reached. Uncertainties present in the food exposure and risk pathway may include the use of residue data from maximum application scenario instead of "typical" pesticide use rate, estimates of the percent of crop treated, and the use of field trial data performed in past years which may not reflect current geographical distributions of pesticide uses. And, although percent of crop treated information collected nationally are highly refined, even more accurate data may be available in the form of the individual company marketing information or data from growers or producers. These uncertainties should be considered as the food exposure pathway is investigated within an aggregate exposure and risk assessment.

B. Drinking Water Pathway: Limitations

In the drinking water pathway, whether using screening-level models to estimate pesticide concentrations in drinking water or the available monitoring data on water quality, there are various sources of uncertainties associated with incorporating data on exposure to pesticides in drinking water into an aggregate exposure and risk assessment. OPP understands that the results provided by the computer simulation models currently used at the first and second tier of analysis for pesticide concentrations in surface water do not characterize either the effects of dilution, distribution and/or potential treatment at a drinking water facility. In addition, the small static pond scenario currently used may not accurately reflect the dynamics in a watershed which is large enough to support a drinking water facility. A further limitation on the results of the surface water models is the lack of documentation and testing of the models in relation to field observations that would allow for judgement as to the models' reliability in predicting pesticide concentration in drinking water. (ILSI, 1998b) Therefore, the models' limitations increase the uncertainty in the semi-quantitative exposure assessment which is based on their results. OPP is developing a model scenario for implementation in early 2000 that more accurately reflects pesticide concentrations in reservoirs that are large enough to be used as a drinking water facility. The SCI-GROW ground-water screening model provides concentration estimates for a pesticide that consistently bound greater than 99% of concentrations for that pesticide in drinking water wells in use areas (Personal communication M. Barrett, USEPA, OPP).

The highest degree of confidence and lowest uncertainty is associated with data representing finished drinking water sampled for specific pesticides known to be highly to moderately used in areas surrounding the drinking water facility. A range of drinking water facilities stratified across those considered to be most vulnerable to contamination to those considered to be more typical would be included in a data set associated with a high level of confidence. For surface water, these vulnerable areas are represented by small- to medium-sized watersheds in agricultural areas that are heavily cropped. For groundwater, agricultural areas with shallow depths to potable

ground water, coarse or sandy soils, and high recharge rates are considered vulnerable to contamination from pesticides.

C. Residential Pathway: Limitations

In the residential exposure pathway, the ability to reconcile environmental measurements, human activity patterns that contribute to potential exposure, and the biological factors that ultimately lead to absorbed dose presents unique challenges for exposure assessors attempting to estimate non-dietary, residential exposure, under the FQPA. Many of the current estimates (post-application in particular) are made in the absence of formal guidance by the Agency. Although the Agency's Office of Research and Development is conducting and designing studies to support post-application and residential model development, the results of those studies are likely to be unavailable for the immediate future. Similar exposure studies to be generated by industry task forces are also in the design phase.

The current, post-application residential exposure models addressing re-entry onto treated lawns and carpets are simple algorithms. Estimates (*e.g.*, Guranathan et al., 1998) need to be viewed in the context of available health surveillance data and studies in which biological monitoring was performed following structured activities. Biological monitoring studies such as those of young children living in the immediate vicinity of pesticide treated orchards (Loewenherz *et al.*, 1997, Simcox *et al.*, 1995) can also provide insight regarding the magnitude of residential exposure. While the models discussed above often predicted up to thousands of micrograms of pesticide per kilogram body weight, the available biological monitoring data and health surveillance data suggest much less per kilogram body weight. The Agency is currently evaluating the default assumptions in the available model/algorithms which may inflate exposure estimates.

Estimating residential exposure of the pesticide applicator is more straightforward. To estimate residential handler exposure, Agency exposure assessors use data available in the Pesticide Handler's Exposure Database (PHED). These data are based on guideline studies and other published data concerning methods and quantity of pesticide application. While the data may contain many non-detects, they do address activities that are reasonably well defined. When a specific application scenario does not exist in PHED or other available databases, exposure assessors estimate the quantity of pesticides that residents use to treat their homes, lawns and gardens, and how often are those applications made using surrogate data and assumptions. Some of the questions surrounding an unmeasured application scenario can be answered through the use of data available though marketing services, company data, or well designed surveys. To the extent that data are not available for use in estimating a home pesticide applicator's exposure, and estimates based on surrogate use data are used, different types of uncertainty exist.

Post-application exposure following treatment of vegetables is also based on activities that are fairly well defined and based on models designed to estimate farm worker exposure. Often, estimates of available residues can be estimated. However, chemical dissipation rates are often unavailable, therefore, allowing only high-end residue estimates. Post-application inhalation

exposure can be addressed using survey data from the National Human Activity Pattern Survey (NHAPS) and well defined ventilation rates available in the Agency's Exposure Factors Handbook (USEPA, 1997b). Surveys such as NHAPS can assign "individuals" to a place for a period of time while conducting a certain activity, *e.g.*, reading a book. Exposure is estimated by comparing an activity, a time duration as reported in NHAPS, and an appropriate (age/weight/gender) ventilation rate from the Exposure Factors Handbook to a residue estimate. But, what is often unknown is airborne concentrations of pesticides following applications and their subsequent dissipation.

VII. Validation and Verification of Aggregate Assessment

A. Model Validation and Verification

In any computer-based simulation/modeling effort, it is essential that the analyst determine that a model is valid, *i.e.*, that the model-predicted result corresponds reasonably well to results obtained in the "real world." Specifically, this requires that a model be both *verified* and *validated*. Model *verification* attempts to verify that the computer simulation is performing as intended and check the translation of the conceptual simulation model into the appropriate computer code. Model *validation*, on the other hand, concerns itself with determining whether the conceptual model is an appropriate simulation of reality and an accurate representation of the system under study (Law and Kelton, 1991).

Any model used to assess aggregate exposure should undergo both model verification and validation (including peer review) to establish the credibility of the model and determine that the model output (*i.e.*, the model predictions) are adequately representative of reality. This stage of model evaluation should also include identification of the model's strengths and limitations as well as the most critical parameters and assumptions used by the model. The validity and credibility of any aggregate exposure model can be investigated by comparing model predictions (in terms, for example, of the *distribution* of daily exposures, expressed in mg pesticide/kg body weight) with the exposure distributions as predicted by a variety of completed studies such as HHANES/NHANES, various EPA and academic institution data, industry task force studies, and (if available) proprietary data from industry or trade groups.

B. Biomonitoring

Biological monitoring, or biomonitoring, provides a basis for estimating an internal dose by measuring a pesticide and/or its metabolite concentrations in selected body tissues or fluids. Biomonitoring studies are performed by government agencies and measure exposures already incurred; no additional exposures take place. Also, biomonitoring involves sampling only (*e.g.*, blood sample) and no additional health effects are likely to occur from the sampling procedures. When done quantitatively, the internal dose determined from biomonitoring reflects exposures (i.e., absorbed doses) from all possible routes. Since the internal dose calculated from biomonitoring represents exposures from all pathways by all routes, biomonitoring potentially

provides a method of validation for aggregate exposure assessments.

The most appropriate methods for biological monitoring should be chosen based on a thorough knowledge and understanding of the pharmacokinetics of the specific pesticide in humans. Detailed guidance for the design and execution of biological monitoring studies presented elsewhere (US EPA, 1998 and references therein). For certain pesticides, biological monitoring may not be an appropriate validation technique. Consider a particular pesticide that is extensively metabolized to a large number of minor metabolites. Each minor metabolite may be subject to inter-individual variability. The following example illustrates the degree of potential inaccuracy in predicting absorbed doses from minor metabolites. A minor metabolite may represent an average of 2 percent of the absorbed dose with reported values ranging from 0.5 percent to 5.0 percent in human volunteers. Using the average value would require the use of a 50-fold correction factor to calculate an absorbed dose. Conversely, if the 5 percent value is representative, a correction factor of 20-fold would be recommended. It is recommended that a suitable biological monitoring marker metabolite would represent at least 30 percent of the administered dose, with a range of values not exceeding a factor of three in human volunteer studies.

Questions for Public Comment

QUESTIONS FOR PUBLIC COMMENT

1. The draft guidance document describes methodologies for assessing pesticide risks from single exposure pathways (food, residential and drinking water). Are these methodologies complete and satisfactorily described, or are changes/additions recommended?

2. The draft guidance document describes a process for combining pesticide exposures and risk from multiple routes for a given pathway of exposure. Is the process, as described, logical, scientifically defensible, and complete?

3. A basic concept underlying the draft aggregate exposure and risk assessment methodology is that of the individual being exposed through calender time with all model parameters referring back to that specific individual. Is use of this fundamental principle as the basis for the aggregate exposure and risk methodology appropriate and, if not, how should it be modified?

4. The draft guidance document acknowledges the need to understand how exposures co-occur. OPP is developing standards to identify co-dependencies and inter-relationships between events, and recognizes that product marketing data may be available to aid in this task. Are there any suggestions on how OPP can best evaluate and incorporate into its assessments co-occurrences of exposure events?

5. During an aggregate exposure and risk assessment, some specific exposure scenarios may be identified as having a minimal contribution to the total aggregate risk. Is it appropriate to exclude specific exposure scenarios that contribute minimally to the total aggregate risk, and if so, at what risk level should an exposure scenario be dropped from further consideration?

6. In certain cases and with certain pathways, it may not be necessary, advisable, or even possible to develop probabilistic exposure estimates and OPP may simply rely on deterministic (or point) estimates of a pathway-specific exposure instead. When aggregating, it will be necessary to combine the pathway-specific exposure estimates to develop an estimate of *aggregate* exposure. Is OPP's general approach to combining deterministic and probabilistic exposure estimates appropriate? Is not, how should it be modified?

7. The draft guidance document describes three methods for combining risks from the three routes (oral, dermal, and inhalation). The Total MOE (MOE_T) and the Aggregate Risk Index (ARI) are currently being used by OPP. Should OPP continue to use these approaches or should OPP consider using the other described approach?

Appendix I

* These tables illustrate the route, exposure and toxicological information to consider for the (5) types of aggregate exposure assessments proposed in the *Interim* guidance on Aggregate Exposure and Risk Assessment.

1. Aggregate Risk Assessment for Acute Exposures			
Source	Route	Exposure	Hazard Source
Food	Oral	High End	Oral Study
Water	Oral	High End	Oral Study
Residential	Not Included		
Aggregate	Oral	High End	Oral
Express result as:	Oral	% Acute RfD	

2. Aggregate Risk Assessment for Short Term Exposures			
Source	Route	Exposure	Hazard Source
Food	Oral	Average	Oral Study
Water	Oral	Average	Oral Study
Residential	Oral	1 to 7 Day Exposure	Oral Study
	Dermal		Oral or Dermal Study
	Inhalation		Oral or Inhalation Study
Aggregate	All		Oral or Route Specific Studies
Express result as:		MOE_{ST} or ARI_{ST}	

3. Aggregate Risk Assessment for Intermediate Term Exposures			
Source	Route	Exposure	Hazard Source
Food	Oral	Average	Oral Study
Water	Oral	Average	Oral Study
Residential	Oral	7 Days to 3 Months Exposure	Oral Study
	Dermal		Oral or Dermal Study
	Inhalation		Oral or Inhalation Study
Aggregate	All		Oral or Route Specific Studies
Express result as:		MOE_{IT} or ARI_{IT}	

4. Aggregate Risk Assessment for Chronic Exposures			
Source	Route	Exposure	Hazard Source
Food	Oral	Average	Oral Study
Water	Oral	Average	Oral Study
Residential	Oral	>6 Months Continuous Exposure	Oral Study
	Dermal		Oral or Dermal Study
	Inhalation		Oral or Inhalation Study
Aggregate	All		Oral or Route Specific Studies
Express result as:		MOE_{CHRON} or ARI_{CHRON}	

5. Aggregate Risk Assessment for Cancer Risk			
Source	Route	Exposure	Hazard Source
Food	Oral	Average	Oral Study (q_1*)
Water	Oral		Oral Study (q_1*)
Residential	Oral	Life-Time Average Daily Dose	Oral Study (q_1*)
	Dermal		Oral Study (q_1*)
	Inhalation		Oral Study (q_1*)
Aggregate	All		Oral Study (q_1*)
Express result as:		Probability	

GLOSSARY

Absorbed dose: The amount of a substance penetrating across the absorption barriers (the exchange barriers) of an organism, via either physical or biological processes. Synonymous with internal dose. (US EPA, 1992).

Active ingredient (ai): The chemical component of a pesticide formulation or end-use product that is intended to act as a pest deterrent. The biologically active chemical agent in a pesticide product (US EPA, 1997a).

Aggregate dose: the amount of a single substance available for interaction with metabolic processes or biologically significant receptors from multiple routes of exposure.

Aggregate Exposure: the amount of a chemical available at the biological exchange boundaries (*e.g.*, respiratory tract, gastrointestinal tract, skin) for all routes of exposure.

Aggregate exposure assessment: A process for developing an estimate of the extent of a defined population to a given chemical by all relevant routes and from all relevant sources (ILSI, p. A-2).

Aggregate risk: the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a single substance.

Biomonitoring: Measurement of a pesticide or its metabolites in body fluids of exposed persons, and conversion to an equivalent absorbed dose of the pesticide based on a knowledge of its human metabolism and pharmacokinetics (Woollen, 1993).

Cumulative Risk: the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a group of substance sharing a common mechanism of toxicity.

Dislodgeable residue: The portion of a pesticide (which may or may not include its metabolites) that is available for transfer from a pesticide treated surface US EPA, 1997a).

Dose: The amount of a substance available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism (US EPA, 1992).

Dose rate: Dose per unit time (e.g., mg/day). Also called dosage. Dose rates are often expressed on a per-unit-body-weight basis (mg/kg/day). Dose rates may also be expressed as an average over a time period (i.e., lifetime) (US EPA, 1992).

Exposure: Contact of a chemical, physical, or biological agent with the outer boundary of an organism. Exposure is quantified as the concentration of the agent in the medium in contact

integrated over the time duration of that contact (US EPA, 1992).

Exposure assessment: The qualitative or quantitative determination or estimation of the magnitude, frequency, duration, and rate of exposure of an individual or population to a chemical.

Exposure scenario: A combination of facts, assumptions, and inferences that define a discrete situation or activity where potential exposures may occur (US EPA, 1997a).
Intake: The process by which a substance crosses the outer boundary of an organism without passing an absorption barrier, e.g., through ingestion or inhalation. (See also potential dose). (US EPA, 1992)

Level of Comparison: A drinking water level of comparison is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses.

Lowest Observed Adverse Effect Level (LOAEL): the lowest dose at which an adverse effect is seen.

No Observed Adverse Effect Level (NOAEL): the dose at which no adverse toxic effect is seen.

Pathway: The physical course a chemical or pollutant takes from the source to the organism exposed. Also called **exposure pathway** (US EPA, 1992).

Population Adjusted Dose (PAD): the RfD adjusted for the FQPA safety factor

Potential dose: The amount of a chemical contained in material ingested, air breathed, or bulk material applied to the skin (US EPA, 1992).

Reference Concentration (RfC): NOAEL (inhalation)/UF

Reference Dose (RfD): NOAEL/UF

Route: The way a chemical or pollutant enters an organism after contact, e.g., by ingestion, inhalation, or dermal absorption. Also called **exposure route** (US EPA, 1992).

Surrogate data: Substitute data or measurements on one substance (or population) used to estimate analogous or corresponding values for another substance (or population).

Transfer coefficient: Residue transfer rate to humans during the completion of specific activities (e.g., cm^2 per hour), calculated using concurrently collected environmental residue data (US EPA, 1998).

Uncertainty - lack of knowledge about specific factors, parameters, or models.

Uncertainty Factor: uncertainty factors applied to account for inter- and intra-species differences in relation to toxic effects, and uncertainties associated with the data.

Unit exposure: The amount of a pesticide residues to which individuals are exposed, normalized by the amount of active ingredient used.

Uptake: The process by which a substance crosses and absorption barrier and is absorbed into the body (US EPA, 1992).

Variability - differences attributed to true heterogeneity or diversity in a population or exposure parameter.

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